

1980

# [4+2] Cycloadditions in organic synthesis, an approach to the total synthesis of quasimarin

Michael John Taschner  
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(4 + 2) CYCLOADDITIONS IN ORGANIC SYNTHESIS, AN APPROACH TO  
THE TOTAL SYNTHESIS OF QUASIMARIN

Iowa State University

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[4 + 2] Cycloadditions in organic synthesis, an approach  
to the total synthesis of quasimarin

by

Michael John Taschner

A Dissertation Submitted to the  
Graduate Faculty in Partial Fulfillment of the  
Requirements for the Degree of  
DOCTOR OF PHILOSOPHY

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Approved:

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In Charge of Major Work

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For the Major Department

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For the Graduate College

Iowa State University  
Ames, Iowa

1980

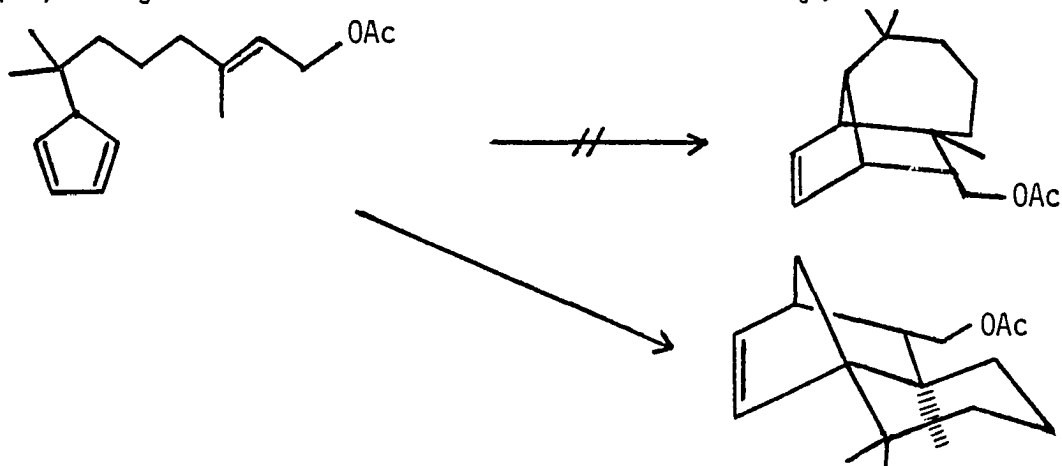
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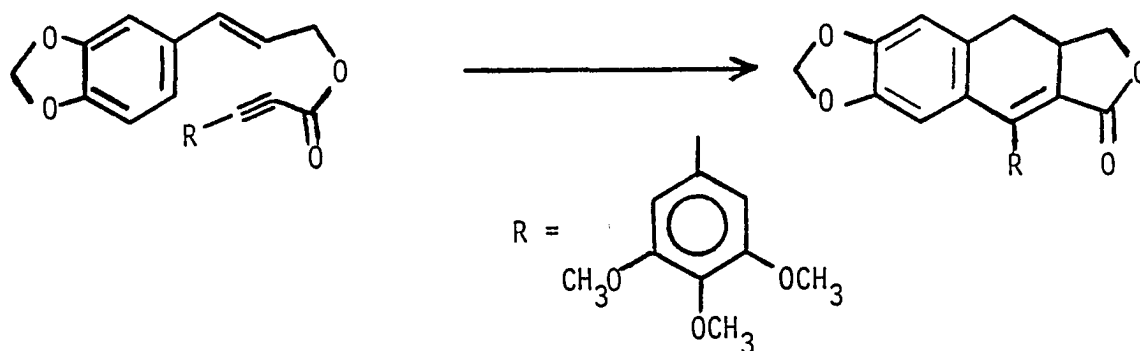
## INTRODUCTION

The  $[4 + 2]$  cycloaddition reaction, more commonly known as the Diels-Alder reaction, has since its discovery in 1928 (1) become one of the most powerful weapons in the arsenal of the organic chemist (2). Its remarkable regioselectivity (3), relatively predictable endo selectivity (4), and syn stereospecificity makes the Diels-Alder reaction unequalled in terms of elegance and efficiency in the construction of six-membered rings. With the recent advances in the syntheses of dienes (5), Lewis acid catalysis (6, 7), and use of high pressures (8) the Diels-Alder reaction should continue to play a major role in preparative organic chemistry.

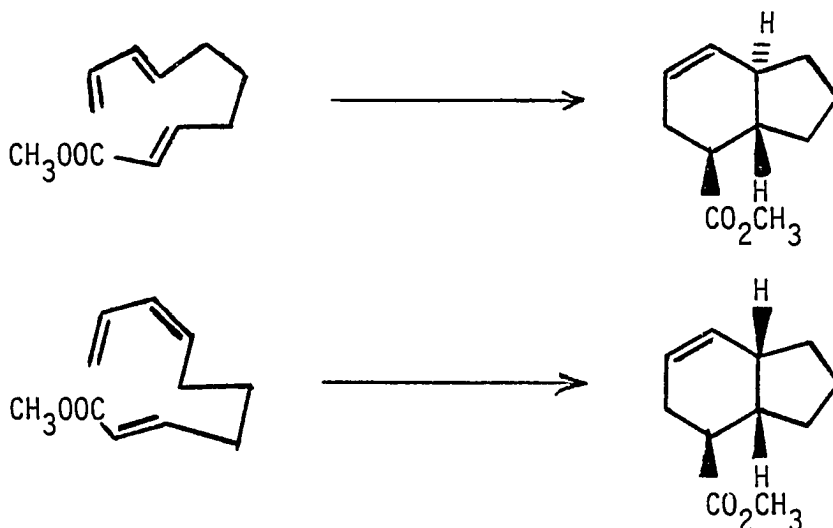
The intramolecular Diels-Alder reaction has recently become an effective method for the synthesis of a variety of interesting polycyclic systems, including many natural products (9). There were several serendipitous examples of intramolecular Diels-Alder reactions prior to 1963 (10). At that time, two groups attempted to apply the reaction to natural products synthesis. Brieger attempted to synthesize longifolene (11) using the reaction shown below. Unfortunately, the desired reaction



pathway was not followed. The other involved the synthesis of a degradation product of podophyllotoxin (12).

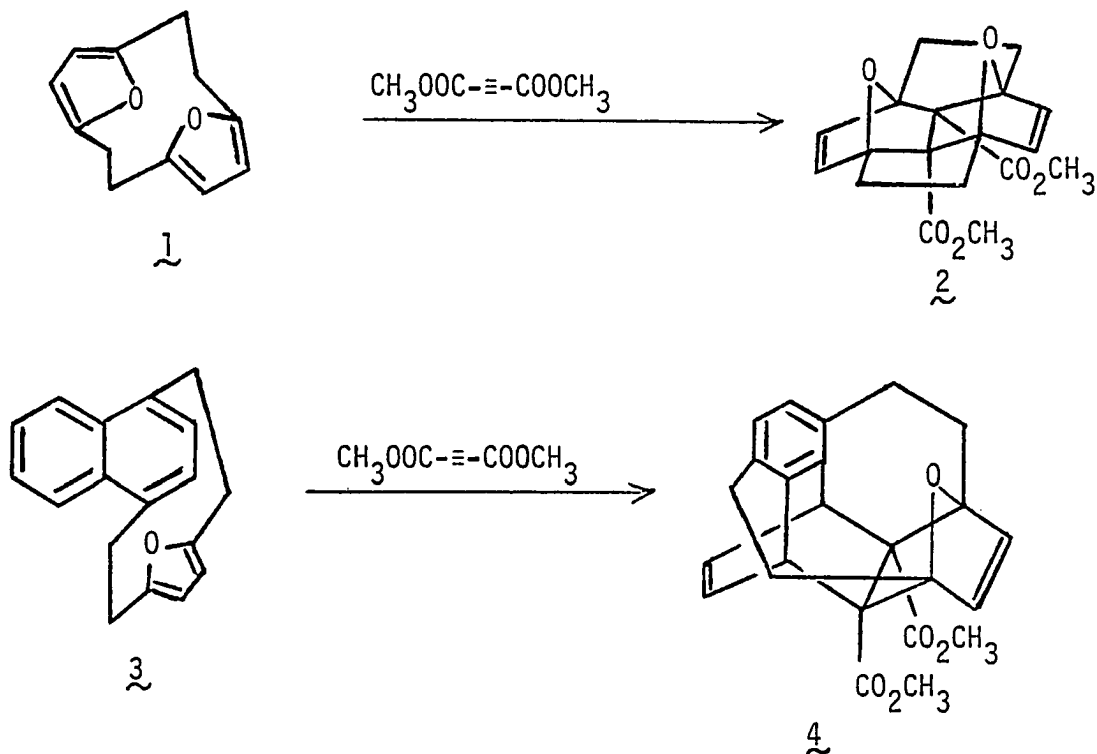


The first systematic investigation of the intramolecular Diels-Alder reaction was performed by House and Cronin in 1965 (13). Methyl trans, trans- and trans, cis-2,7,9-decatrienoates were cyclized regioselectively and stereospecifically to form the tetrahydroindanes shown below.



Cram and Knox, in 1961, demonstrated the viability of performing an intermolecular Diels-Alder reaction followed by an intramolecular Diels-Alder reaction of the initial cycloadduct (14a). The furanophane

1 was reacted with dimethyl acetylenedicarboxylate to produce 2. Wasserman and Kitzing reacted dimethyl acetylenedicarboxylate with naphthalenofuranophane 3 resulting in 4 (15). These reactions were

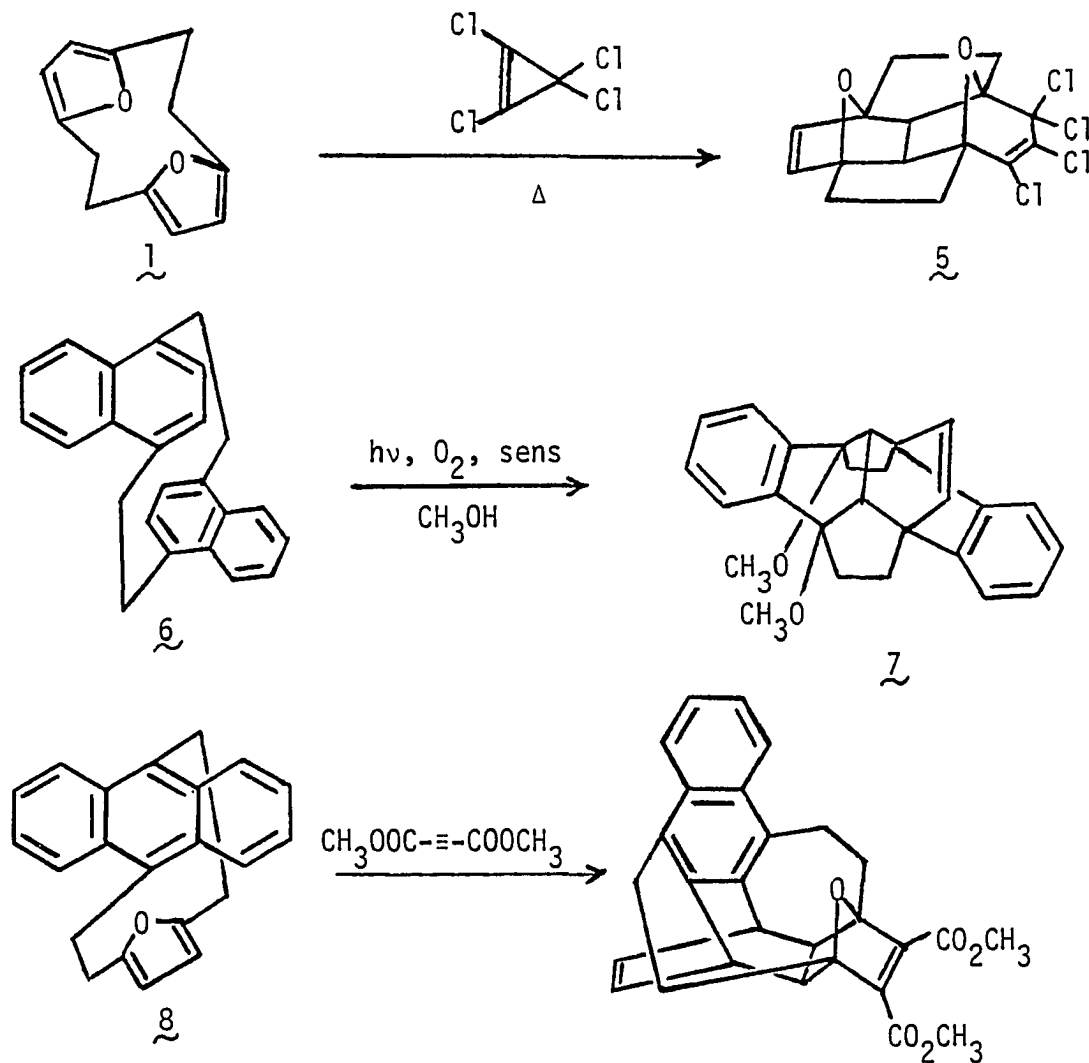


classified as "pincer Diels-Alder reactions". This is an appropriate term since it accurately describes the compression of a dienophile between two diene components. They require the dienophile to originally be acetylenic and utilize both degrees of unsaturation in the triple bond for the two-stage cycloaddition.

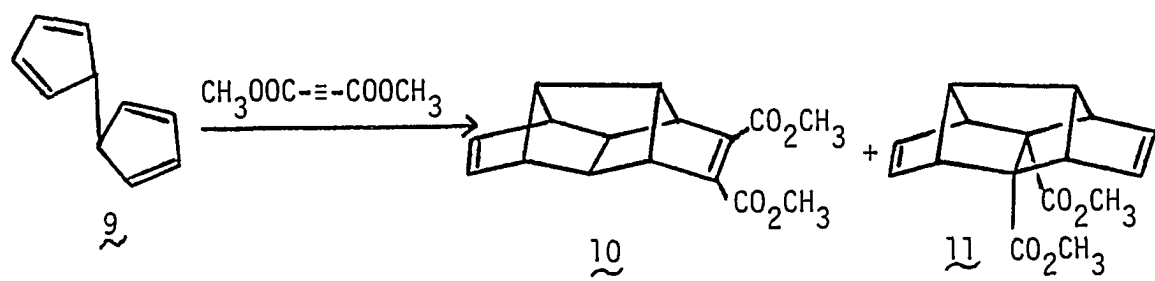
The second way in which this multistage carbon-carbon bond forming reaction can occur is for the new olefinic center generated by the initial intermolecular cycloaddition to become involved as a dienophile in the subsequent intramolecular cycloaddition. Illustrative of this type of reaction are the reaction of furanophane 1 with



tetrachlorocyclopropene to give 5 (16), the reaction of anti-[2.2] naphthalenophane 6 with singlet oxygen in methanol to yield 7 (17), and the addition of dimethyl acetylenedicarboxylate to anthracenophane 8 (18, 19).



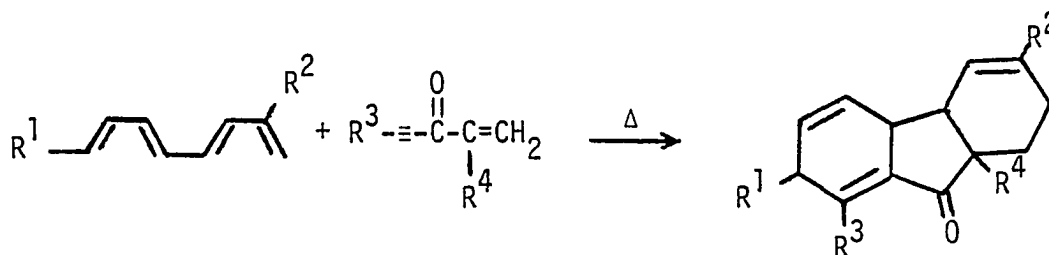
Paquette, et al. have coined the term "domino Diels-Alder reactions" to refer to such processes (20). They reacted 9,10-dihydrofulvalene 9 with dimethyl acetylenedicarboxylate to give 10 and the pincer adduct 11.



## RESULTS AND DISCUSSION

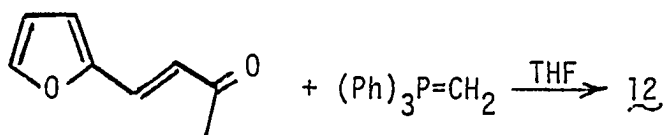
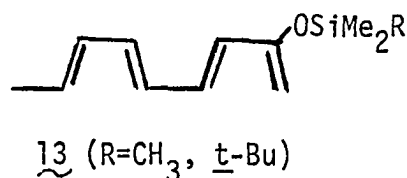
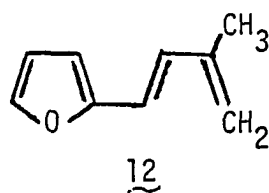
## Timed Diels-Alder Reaction

A third approach to the concept of an intermolecular Diels-Alder reaction followed by an intramolecular Diels-Alder reaction is to have two dienophiles present in one of the reactants and have two dienes in the other. The general features of this novel method are depicted below.

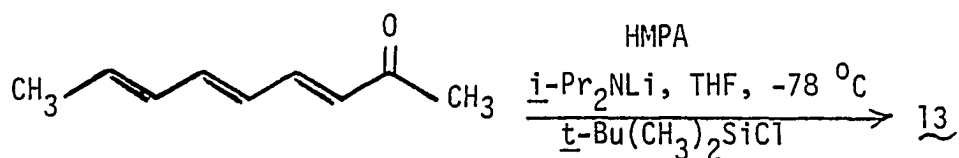


In this polycycloaddition (termed a "timed Diels-Alder") (21) a tricyclic ring system is formed regiospecifically in a single reaction. In principle, a number of compounds might be formed. However, one of the diene units in the bis-diene is more reactive than the other unit. The same feature is true for the bis-dienophile. Thus, the initial ring is created by cycloaddition of the more reactive diene and dienophile. The second and third rings are formed by the intramolecular cycloaddition of the less reactive diene and dienophile.

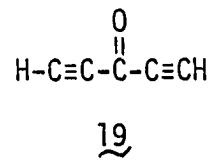
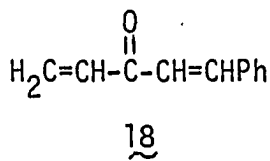
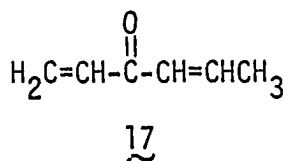
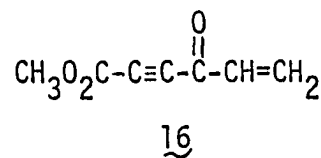
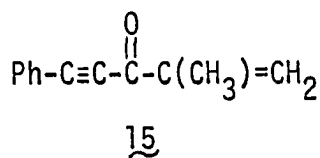
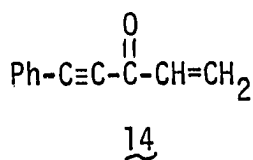
The bis-dienes used in this investigation were compounds 12 and 13. The preparation of 12 was readily accomplished by the use of a Wittig reaction on 4-(2-furyl)-3-buten-2-one (22). It could be purified by bulb to bulb distillation or by filtration through silica gel. Bis-diene 13 could be synthesized by trapping the kinetic anion of



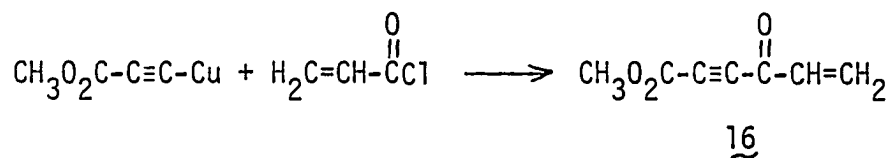
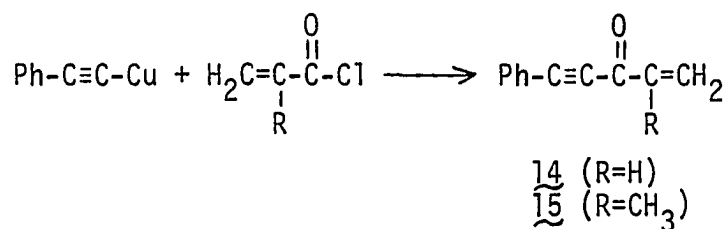
3,5,7-octatrien-2-one (23) with chlorotrimethyl-*tert*-butylsilane or chlorotrimethylsilane. Both bis-dienes were unstable to prolonged storage but could be stored for days under an inert atmosphere at 0 °C.



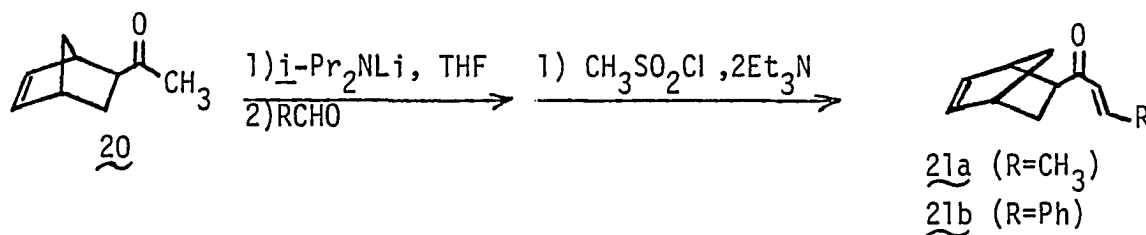
The array of bis-dienophiles employed in this study consisted of enynones 14, 15 and 16, dienones 17 and 18, and diynone 19. The enynones 14 and 15 were made by the coupling of cuprous phenylacetylide



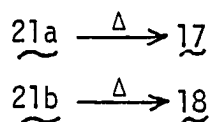
with the requisite acid chloride according to the method of Normant and Bourgain (24). Enynone 16 was similarly prepared. Dienones 17 and 18



were efficiently synthesized from ketone 20 by aldol condensation, dehydration and retrograde Diels-Alder reaction. Dehydration could be



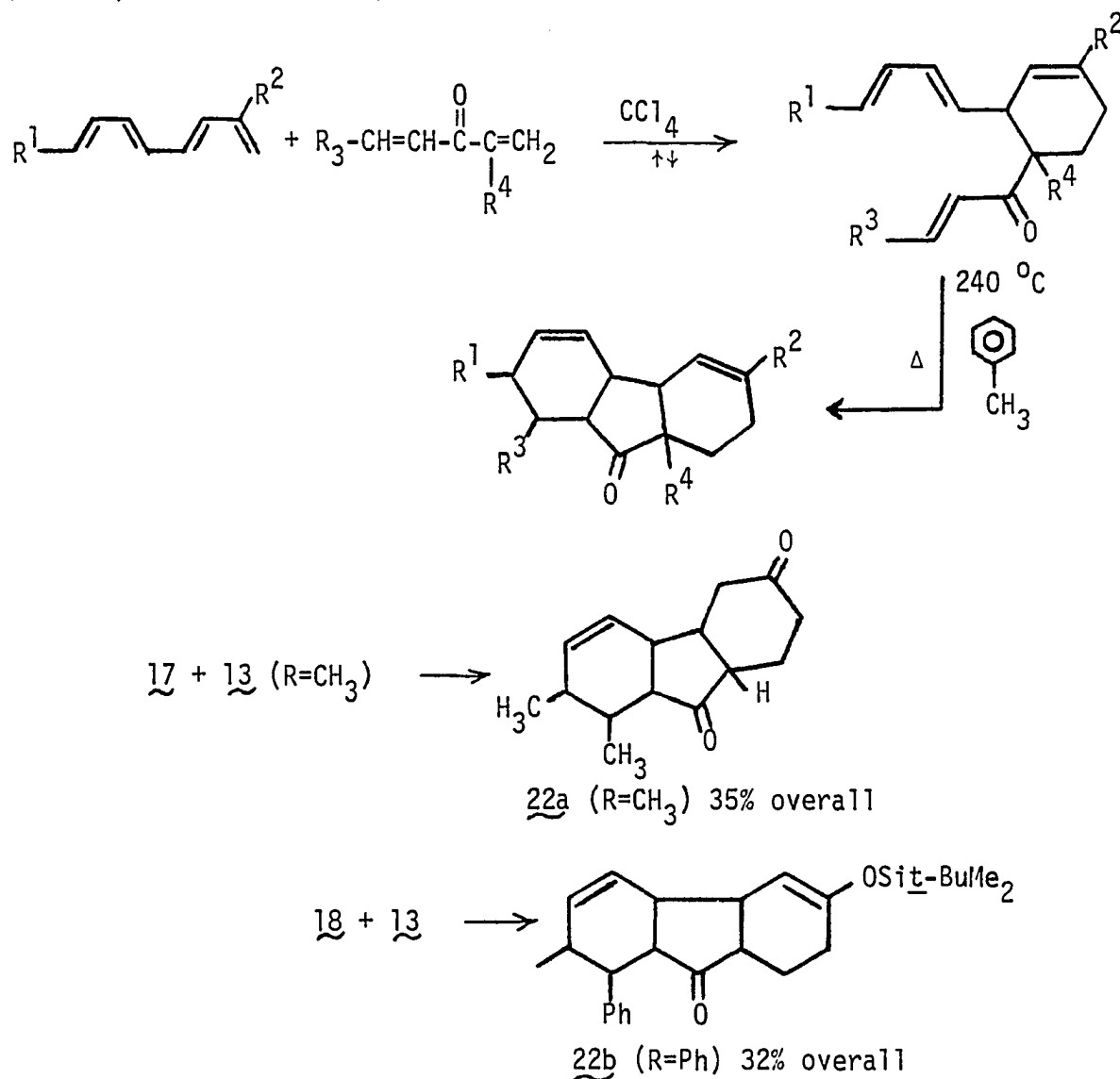
most effectively accomplished by mesylation followed by reaction with triethylamine (25) to form 21a or 21b. Compounds 21a and 21b were then subjected to flow pyrolysis conditions (600 °C/20 mm) to afford dienones 17 and 18. Dienone 19 had been previously prepared (26).



### Diels-Alder reactions

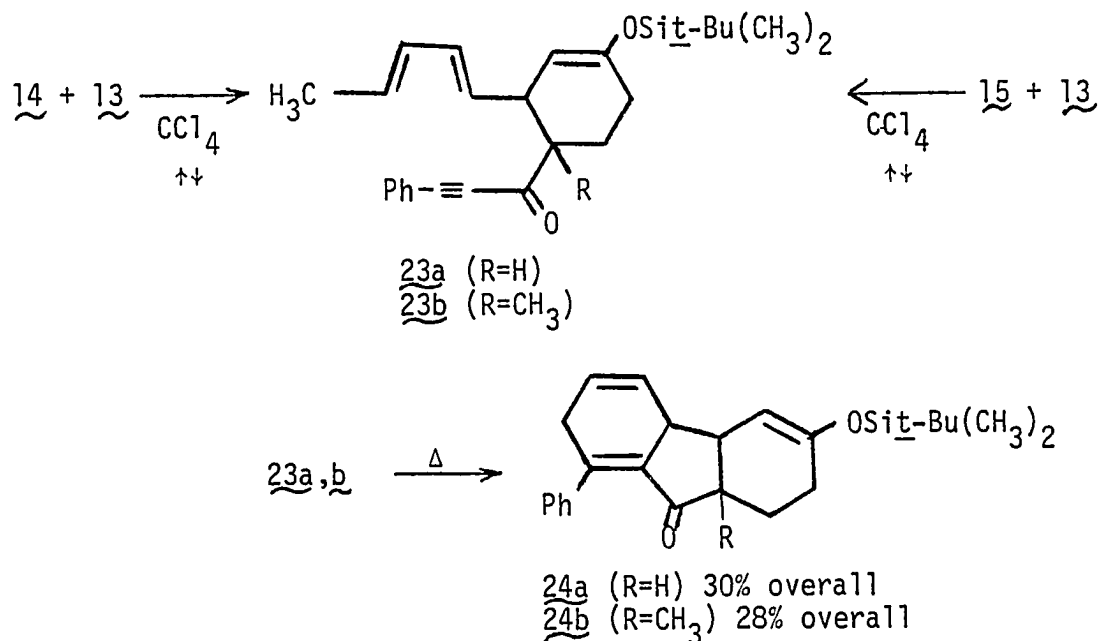
The optimal conditions for the polycycloaddition reaction were found to be the reaction in refluxing CCl<sub>4</sub> to form the first cyclohexene ring followed by a sealed tube reaction at elevated temperatures to effect closure to the tricyclic system. No tricyclic product was obtained after

reaction at ambient temperature for one week. If the reactants were simply heated at 240 °C, the yield of the desired tricyclic structure was greatly reduced due to polymer formation. The results with dienones 17 and 18 and bis-diene 13 are illustrated below. The proposed structure

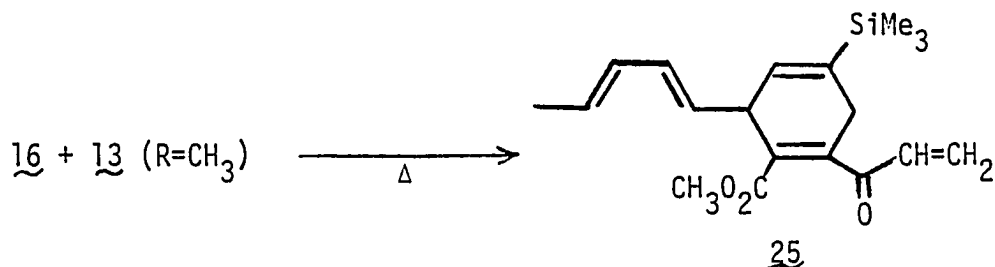


of 22a is supported by infrared absorptions at 1720 and 1740 cm<sup>-1</sup>. Similar information (absorption at 1735 cm<sup>-1</sup>) can be obtained from the spectra for 22b. Both compounds are homogeneous by thin layer chromatography.

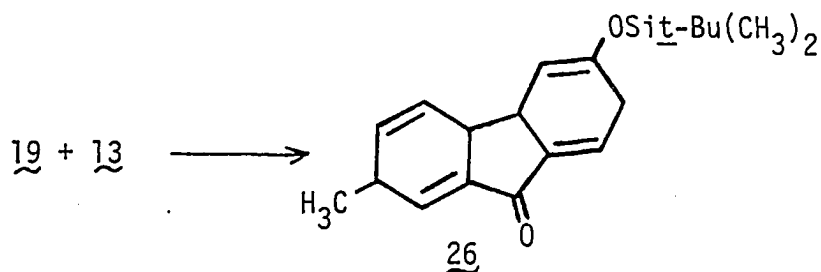
Enynones 14, 15 and 16 undergo Diels-Alder reaction with 13 as illustrated below. Cyclohexenes 23a,b show absorptions corresponding



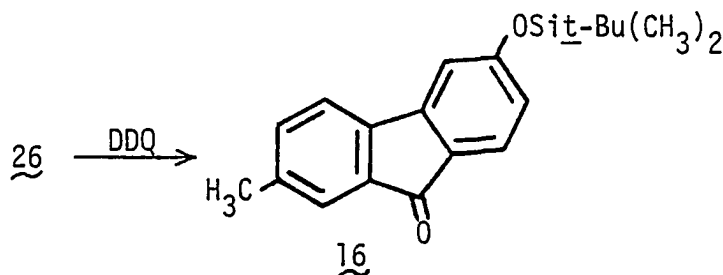
to ynones ( $2200 \text{ cm}^{-1}$ ,  $1620 \text{ cm}^{-1}$ ). The NMR spectra indicate the absence of enone hydrogens. After thermal cyclization, compounds 24a or 24b are obtained. The infrared spectra of both 24a and 24b lack the intense acetylenic absorption characteristic of 23a and 23b. In contrast to the behavior of enynones 14 and 15, the Diels-Alder reaction of 16 with bis-diene 13 afforded only mono addition to yield 25. In this case the



orientation was governed by the directing effects of the carbomethoxy group. The Diels-Alder reaction of diynone 19 with 13 presented unexpected difficulty because of the instability of the monocyclic adduct at elevated temperatures. The optimal conditions for cyclization involved heating the reactants in warm carbon tetrachloride overnight. Adduct 26 could be smoothly dehydrogenated to the fluorenone with DDQ (27).

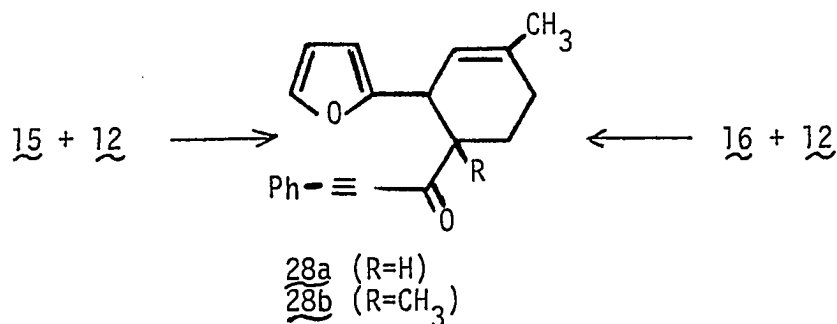


Compound 27 exhibited the ultraviolet and infrared spectra characteristic of a 3-alkoxyfluorenone. Both high resolution and low resolution mass spectroscopy also support the assigned structure.



The Diels-Alder reactions of bis-diene 12 with enynones 15 and 16 proceed only to the monocyclic compound. No conditions could be found for the cyclization of monoadduct 28a or 28b. While this work was





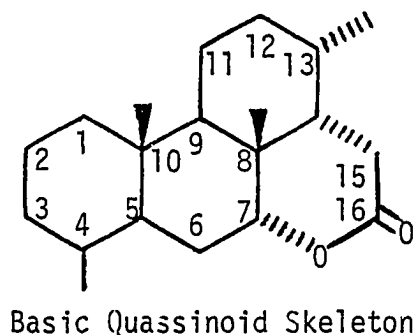
in progress, Parker and Adamchuk (28) recently published results on simpler systems which support our observations.

From the results presented above, it is clear that a delicate balance between relative reactivity and the directing effects of substituents on the bis-diene is involved for the successful cycloaddition. If one of the diene units in the bis-diene is unreactive or if an unfavorable equilibrium exists between adduct and uncyclized compound, this polycycloaddition concept cannot be used successfully. Another interesting facet of this reaction is the control of stereochemistry. In the cycloaddition between 13 and a dienone, six chiral centers are created, whereas between 13 and an enynone only four chiral centers are developed. The assumptions of a concerted cycloaddition and the well-documented preference for endo addition limit the number of possible permutations which can be obtained. An analysis of stereochemistry must begin with a study of the initially-formed adduct, since the stereochemistry created in the monocyclic structure might be expected to direct the development of the remaining asymmetric centers (9b). In the case of adduct 23b, the NMR spectra indicated only one methyl singlet present in the aliphatic region (29).

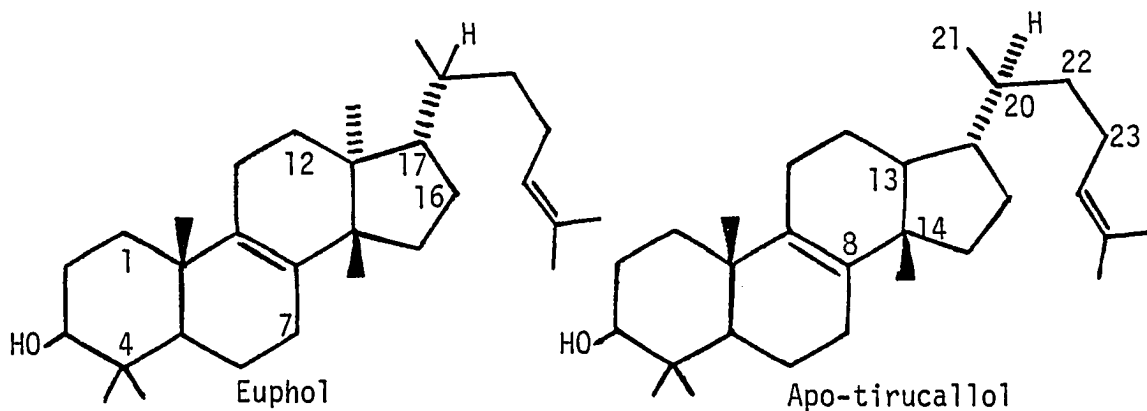
After thermal cycloaddition to the adduct 24b, however, the  $^{13}\text{C}$  NMR of purified product indicated that a mixture of stereoisomers was formed. Analysis of the  $^{13}\text{C}$  spectra of adduct 22b also indicated that an isomeric mixture had been obtained.

### The Quassinoids

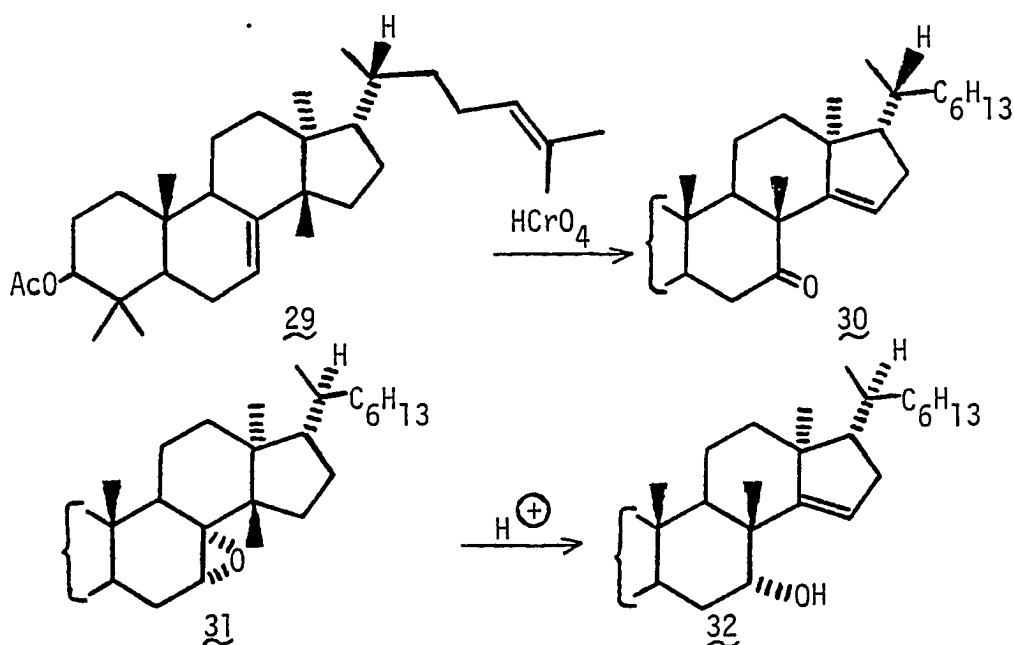
We next sought to extend the "timed Diels-Alder reaction" to the synthesis of a group of natural products known as the quassinoids (30), in particular, quasimarin (31) and bruceantin (32). Most of the quassinoids are  $\text{C}_{20}$ -compounds and have the basic skeleton shown below.



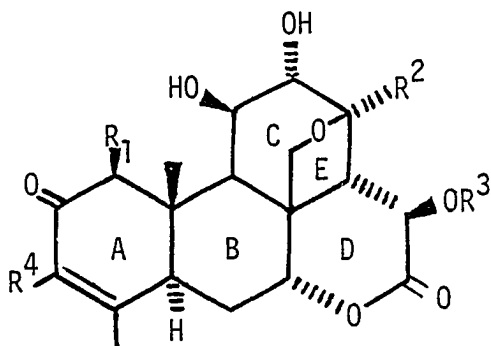
The quassinoids are formed by the biogenetic degradation of the triterpenoids euphol ( $20\ \beta\ \text{H}$ ) or apo-tirucallol ( $20\ \alpha\ \text{H}$ ) (33). It can be



seen that one of the methyl groups at C-4 and four carbon atoms at the end of the side chain have been eliminated and carbons C<sub>20</sub>-C<sub>23</sub> have been converted to a  $\delta$ -lactone. Also the C-14 methyl group undergoes a cationic migration to C-8. Evidence for such rearrangements is provided by the chromic acid oxidation of 29 to 30 and the rearrangement of the  $\alpha$ -epoxy derivative 31 to 32 (34).



A number of the quassinoids are well-known in herbal medicine as antiamoebic agents (35). Quasimarin (31) 33a and bruceantin (32) 33b are potential antitumor agents recently isolated from Quassia amara and Brucea antidysenterica, respectively. Both have shown in vitro activity against human carcinoma of the nasopharynx (KB) at the  $10^{-3}$   $\mu\text{g/mL}$  level and inhibitory activity against the P-388 lymphocytic leukemia in the mouse over a broad dosage range at the  $\mu\text{g/kg}$  level. Bruceantin has also shown activity against Walker 256 intramuscular carcinosarcoma

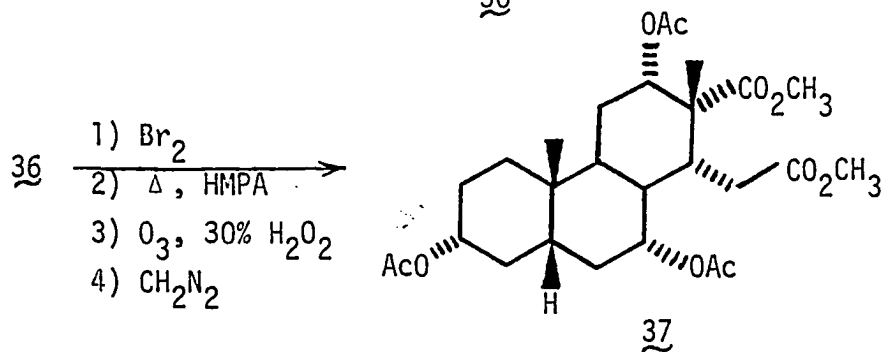
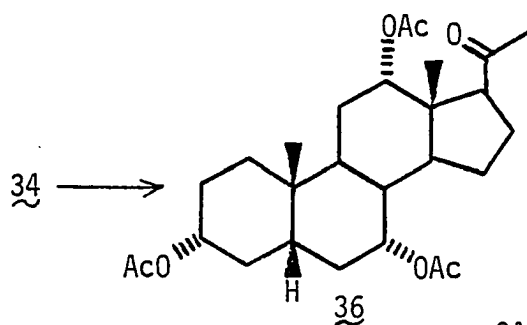
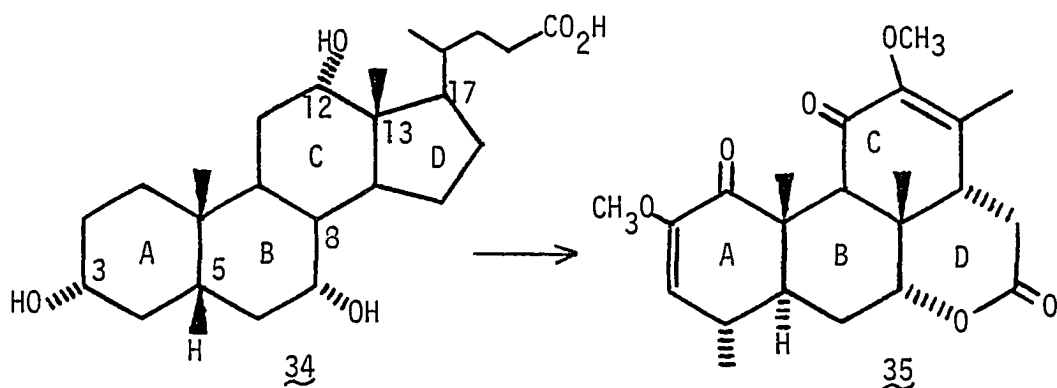


- 33a ( $R^1=OH$ ;  $R^2=CH_3$ ;  $R^3=COC(OAc)(CH_3)Et$ ;  $R^4=H$ )  
33b ( $R^1=H$ ;  $R^2=CO_2CH_3$ ;  $R^3=COCH=(CH_3)(i-Pr)$ ;  $R^4=OH$ )

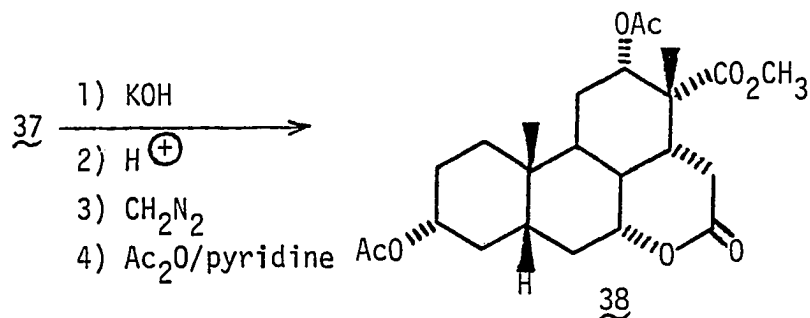
and L-1210 lymphoid leukemia. The activity of bruceantin against two murine tumor systems, a property not common in antitumor compounds, is of perhaps greatest interest (32). Most of the clinical work has been done with bruceantin but quasimarin should show comparable activity.

There have only been a limited number of synthetic assaults on the quassinoid skeleton. One approach involved the chemodestruction of a steroid nucleus (36). An annelation sequence was employed in an aborted endeavor (37). There was a model system synthesis of the BCE ring system of bruceantin (38). Two more successful approaches by Valenta, et al. (7f, 39) and Grieco, et al. (40) utilized a Diels-Alder strategy to construct the quassinoid skeleton.

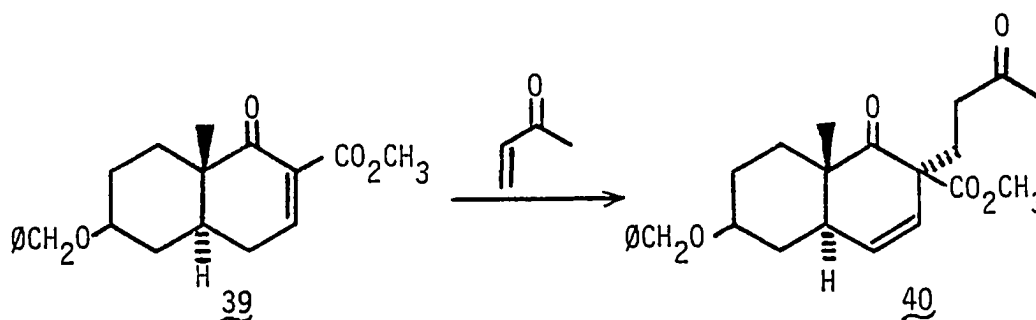
The basic plan of the degradation scheme was to convert cholic acid 34 to quassin 35 (36). All the work to date has centered around the conversion of the D-ring of cholic acid to the  $\delta$ -lactone. This was accomplished by first converting cholic acid to the methyl ketone 36. Ketone 36 was then transformed in a series of four steps to the diester 37. Compound 37 was submitted to saponification, lactonization,



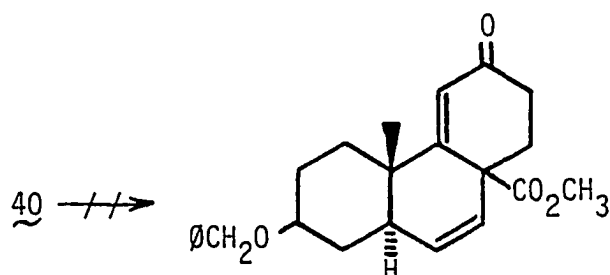
esterification, and acetylation to provide 38. The  $\delta$ -lactone has been constructed but the molecule lacks a methyl group at C-8 and C-4 and the configuration at C-5 is wrong. Although there is oxygen functionality in all of the rings to use as handles for further transformations, the route will undoubtedly be long and tedious.



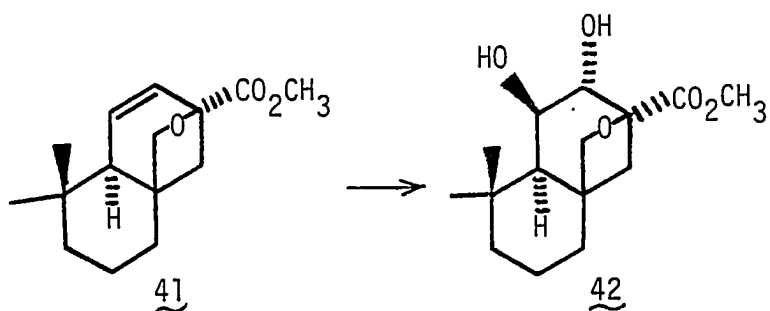
In an assault on bruceantin 33b, Snitman, et al. envisioned the C ring arising from the Robinson annelation of methyl vinyl ketone and 39 (37). The Michael addition of 39 with methyl vinyl ketone



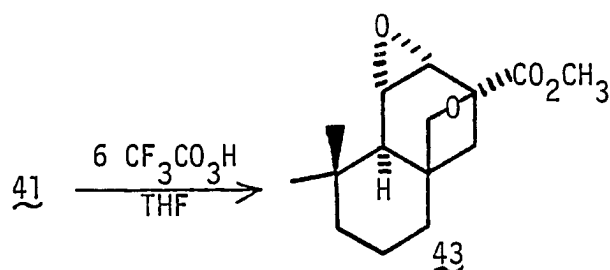
worked well but no conditions could be found to affect the final aldol cyclization. For this reason the route was abandoned.



Dailey and Fuchs designed a model system of bruceantin to study the feasibility of converting cyclohexene 41 to the trans-diaxial diol 42 (38). The most direct and efficient route would have involved

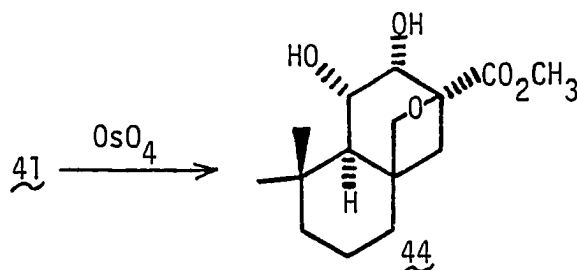


epoxidation and acid catalyzed opening of the epoxide. The molecule, however, would have no part of any such transformation. Compound 41 was reluctant to epoxidize with m-chloroperoxybenzoic acid. Success was finally realized by using 6 equivalents of peroxytrifluoroacetic acid.

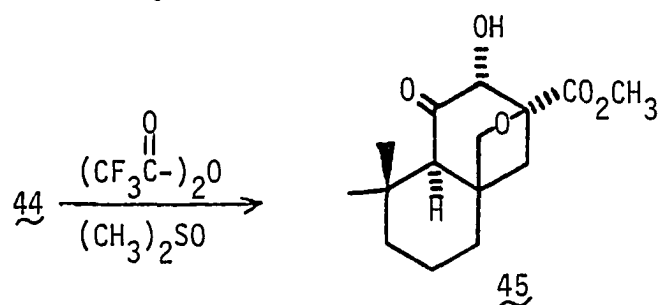


Attempts to open the epoxide 43 under a variety of conditions led to rearrangement or elimination products. None of the trans-diaxial diol 42 could be detected.

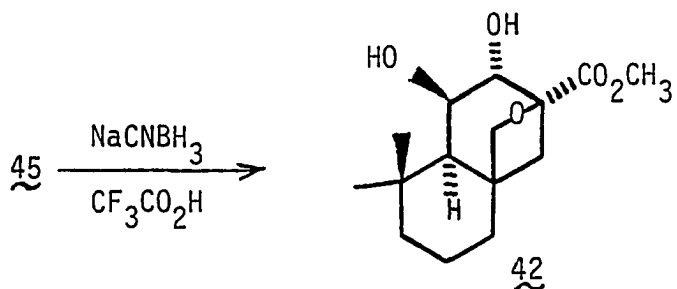
A circuitous route to diol 42 was then devised. Olefin 41 was hydroxylated with osmium tetroxide to produce the cis-diol 44.



Selective oxidation of the equatorial alcohol in 44 using trifluoroacetic anhydride and dimethyl sulfoxide furnished the keto alcohol 45.



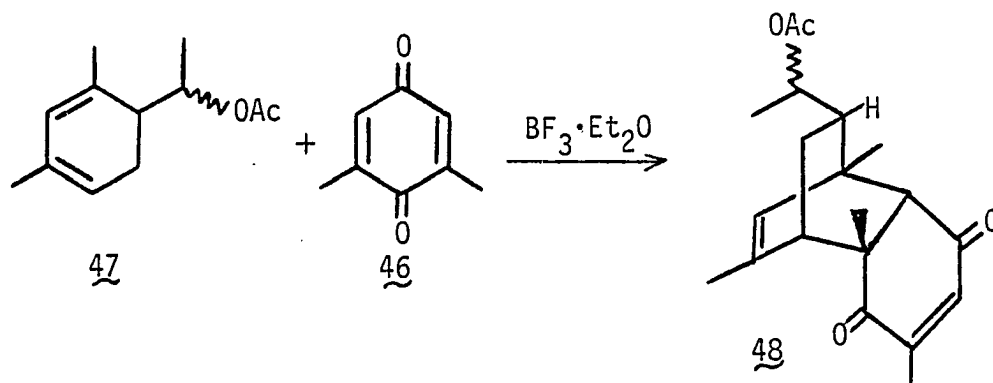
Reduction of 45 with sodium cyanoborohydride in trifluoroacetic acid resulted in the formation of the trans-diaxial diol 42. They finally



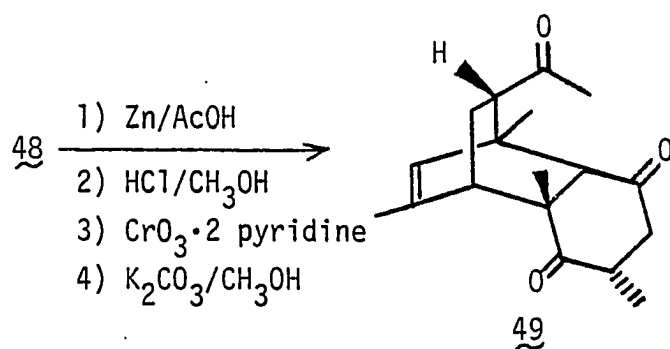
do succeed in producing the trans-diol but the molecule has absolutely no chance of being taken on to the final target. The molecule even has a drawback as a model system. There is no substituent which mimics the  $\delta$ -lactone moiety. This feature would seem key to the model system in order to determine what effects an axial side chain would have on approach of reagents from the  $\alpha$ -face of the molecule.

Valenta, et al. make use of a Lewis acid catalyzed orientation reversal Diels-Alder reaction (7f, 39). Reaction of quinone 46 and diene 47 in the presence of boron trifluoride etherate yielded the tricyclic molecule 48 as a 1:1 mixture of acetates. Acetate 48 was

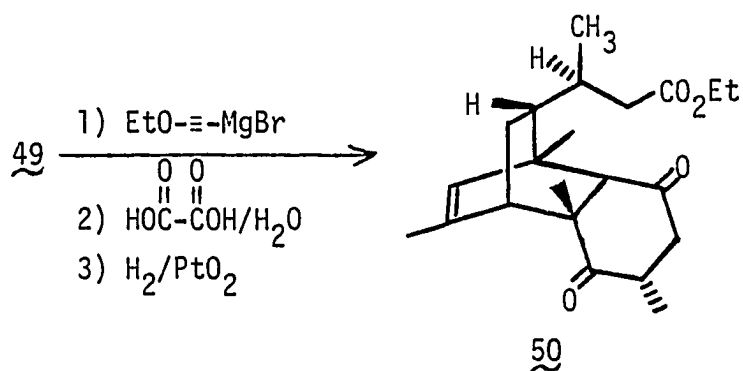




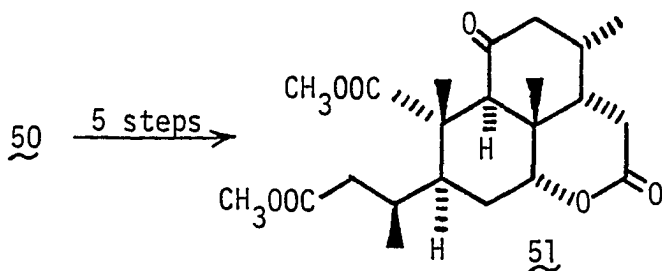
reduced, saponified, oxidized, and epimerized to yield methyl ketone 49.  
Conversion of 49 to the diketo ester 50 by treatment with ethoxyethynyl



magnesium bromide, aqueous oxalic acid, and hydrogenation results in the formation of a compound containing all the skeletal carbon atoms of quassin 35 and all the nonepimerizable chiral centers in correct relative configurations.

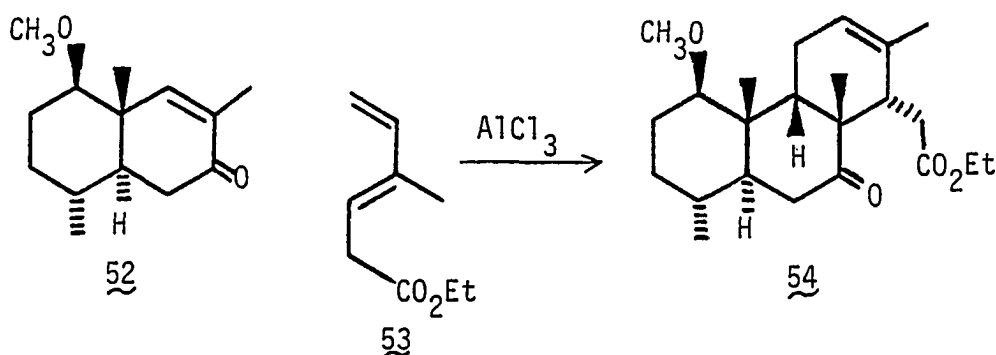


Compound 50 was transformed into a seco-derivative of quassin in five steps in excellent overall yield (39). In order to complete

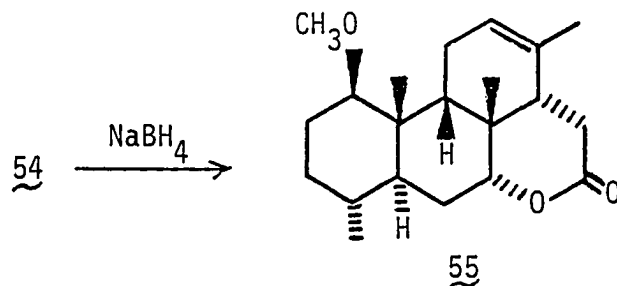


the synthesis is formation of the A-ring and final manipulation of the oxidation state of the C-ring. Once this is accomplished, the route will serve as an excellent example of how to control the stereochemistry of various centers relative to one another.

Another Lewis acid catalyzed Diels-Alder strategy was employed by Grieco, et al. in their approach to quassin 35 (40). Reaction of enone 52 with diene 53 in the presence of 0.25 equivalents of aluminum tri-chloride resulted in the formation of 54 as the sole Diels-Alder product.



Ketone 54 was reduced with sodium borohydride to furnish lactone 55. The structure of 55 was confirmed by single-crystal X-ray analysis. Lactone 55 has reportedly been taken on to quassin 35 (41).

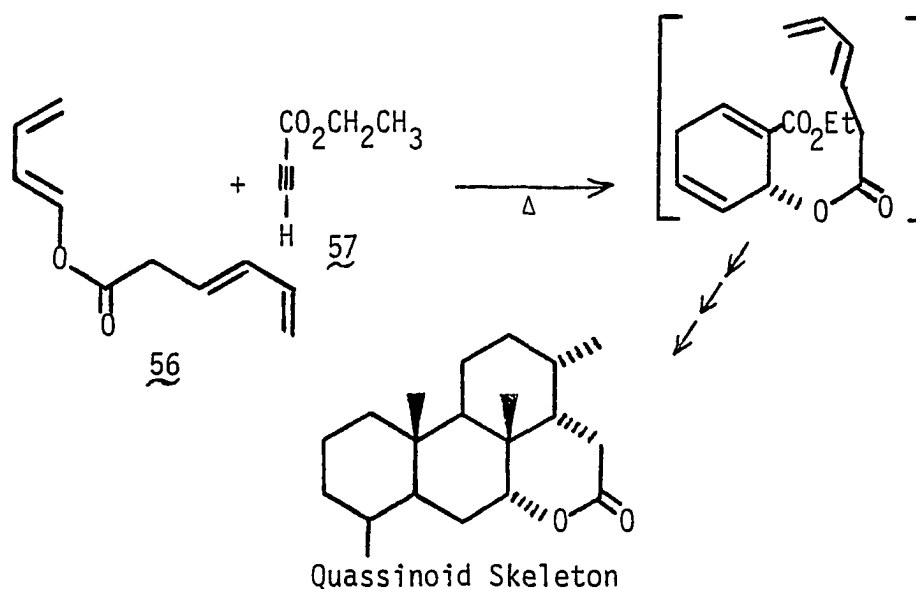


It should be noted that neither of these last two strategies can be applied to the synthesis of quasimarin 33a or bruceantin 33b. They both lack the hydroxymethyl functionality necessary for the formation of the five-membered ring ether (ring E). The route of Valenta, et al. (7f, 39) could not be adapted to introduce such functionality without suffering severe consequences in the regiochemical control of the initial Diels-Alder reaction. The second approach by Grieco, et al. (40) has a better chance of incorporating the necessary functionality. However, the use of a hydroxy methyl enone derivative of 52 may result in failure of the Diels-Alder reaction for steric reasons. Substitution of an ester for the  $\alpha$ -methyl group of enone 52 could cause a reversal in the stereochemical outcome of the Diels-Alder. These two routes will undoubtedly encounter a number of problems if they are to be extended to incorporate molecules such as quasimarin and bruceantin.

#### Approach to the Quassinoid Skeleton

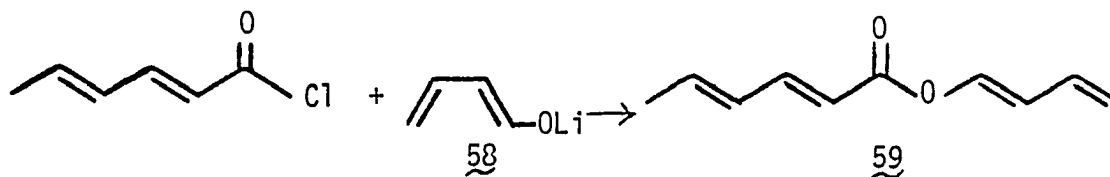
Although there has only been a limited amount of work on the synthesis of quassinoids, it can be noted that a Diels-Alder strategy is vital for a convergent and successful synthesis. Our original

approach to the quassinoid skeleton was to apply the "timed Diels-Alder reaction". The synthetic target was envisioned to arise from the bis-diene 56 and the acetylenic ester 57. At first glance, it appears as

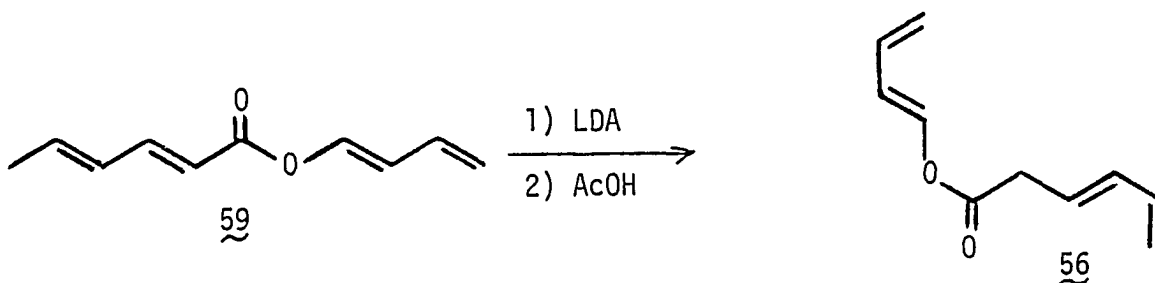


though this reaction might best be described as a "pincer Diels-Alder reaction". Careful scrutiny, however, will reveal that the reaction lies more in the realm of the "timed Diels-Alder reaction". The acetylene is not really being compressed between two dienes and the dienes are sufficiently biased as to allow selective reaction of one prior to the other.

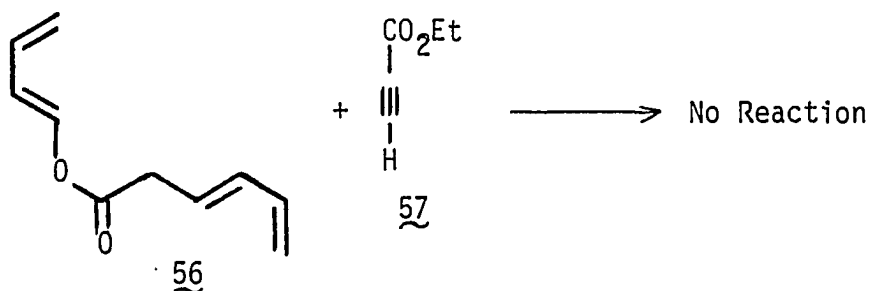
To test the hypothesis, the synthesis of bis-diene 56 was undertaken. The reaction of sorbyl chloride with dienolate anion (42) 58 yielded crystalline (mp 59 °C) ester 59. Deconjugation of ester 59



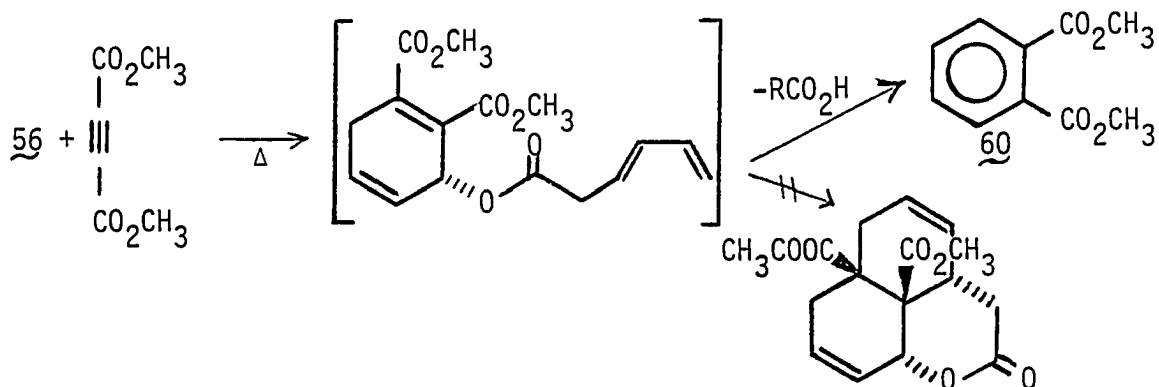
was achieved using lithium diisopropyl amide (43). Quenching with acetic acid resulted in the formation of bis-diene 56 in 91% yield.



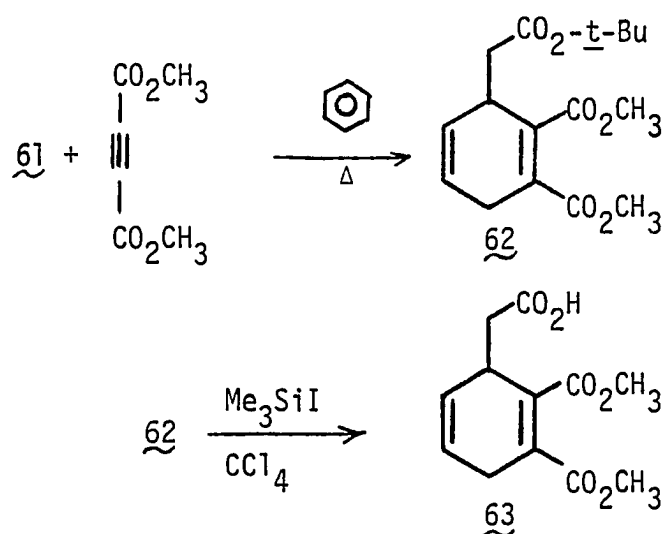
No conditions could be found to effect any cyclization between the acetylenic ester 57 and bis-diene 56 without the annihilation of bis-diene 56. Under the assumption the dienophile was not reactive enough,



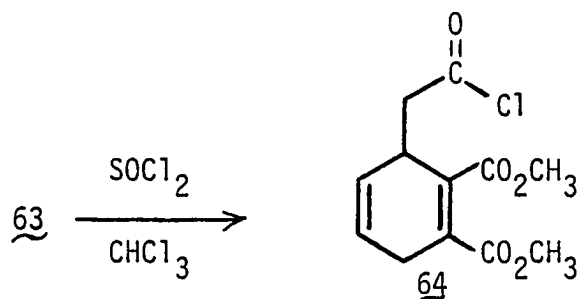
dimethyl acetylenedicarboxylate was employed. The dienophile was reactive enough in this case to add to the sorbyloxyl butadiene portion of 56. Instead of undergoing the intramolecular Diels-Alder reaction, the molecule eliminated sorbic acid (or the deconjugated sorbic acid) to produce dimethyl phthalate 60. The next option was to attempt to remove the possibility for the molecule to aromatize. To investigate the viability of this plan, dimethyl acetylenedicarboxylate was reacted with deconjugated t-butyl sorbate 61 to produce cyclohexadiene



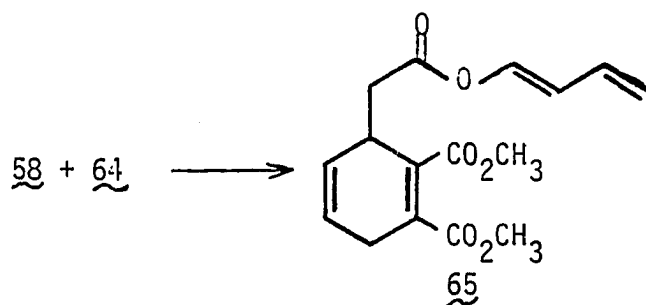
**62** in 79% yield. Selective hydrolysis of the *t*-butyl ester, in the presence of the methyl esters, was accomplished utilizing trimethylsilyl



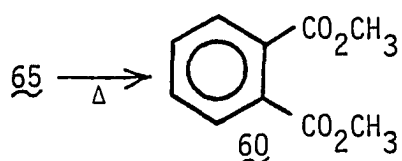
iodide (44). The resulting acid, **63**, was converted to acid chloride **64** with thionyl chloride in quantitative yield. Reaction of acid



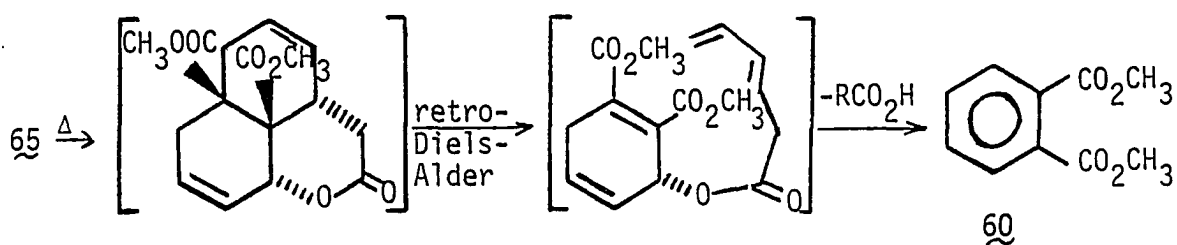
chloride 64 with the dienolate anion 58 produced the dienol ester 65 in 87% yield. Compound 65 appears to be set to perform the intramolecular



Diels-Alder reaction without incident. However, the only product observed from the thermolysis of 65 was once again dimethyl phthalate, 60. This was most likely the result of the desired intramolecular

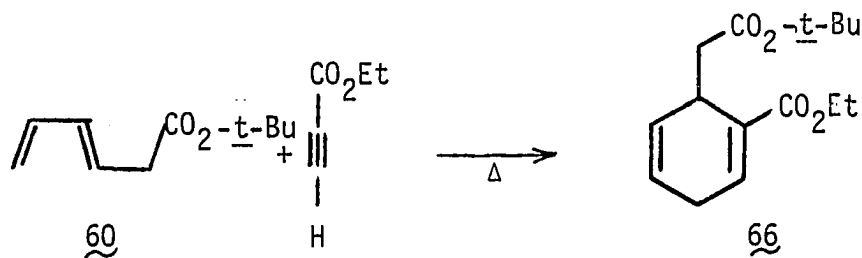


reaction followed by a retro-Diels-Alder reaction and once again elimination of the acid to aromatize the diester. No conditions could

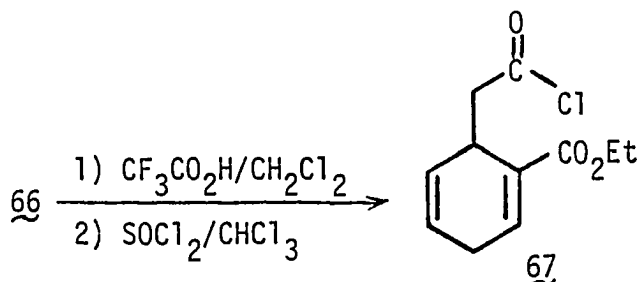


be found which would allow the intramolecular Diels-Alder reaction without the ensuing retro-Diels-Alder reaction.

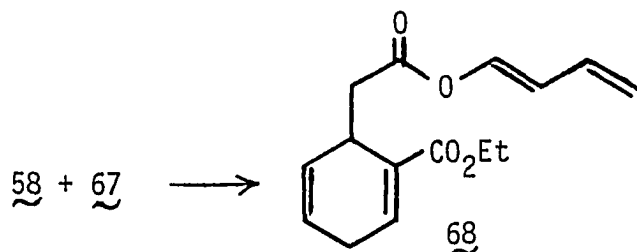
In the hope the cis-diester which would result from the second cyclization was causing unforeseen steric problems, it was decided to remove one of the esters. This was most easily accomplished by exchanging ethyl propiolate for dimethyl acetylenedicarboxylate in the initial Diels-Alder reaction with diene 60. Cyclohexadiene 66 was converted



to acid chloride 67 by reaction with trifluoroacetic acid; followed by treatment of the acid with thionyl chloride. Dienol ester 68 was

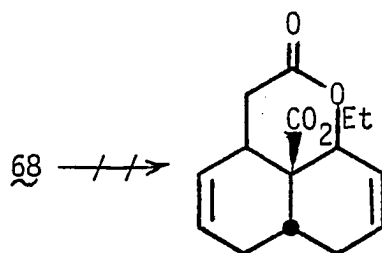


prepared by the reaction of anion 58 with acid chloride 67. Compound 68 could not be induced to undergo the desired intramolecular



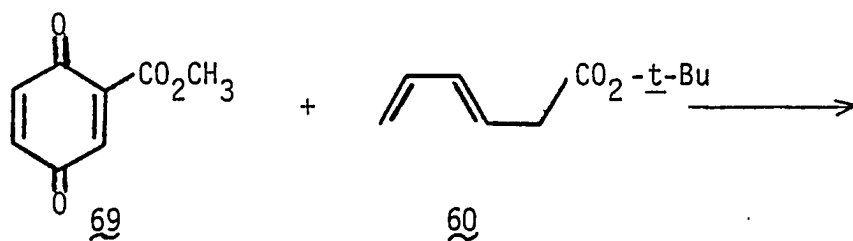


cyclization. A variety of conditions led to recovered starting material or unidentifiable products.

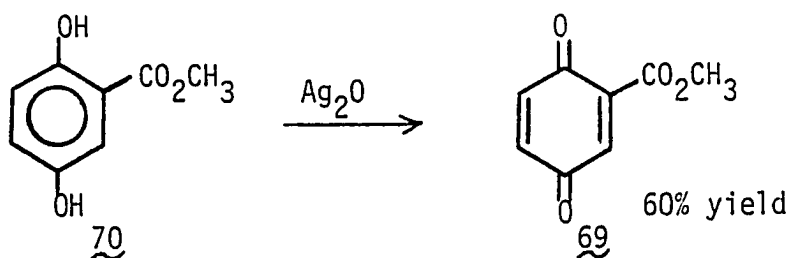


### In Situ Diels-Alder Reaction

Undaunted, the quest for a synthetic approach to the quassinoids continued with the reaction of quinone 69 and diene 60. Quinone 69 was

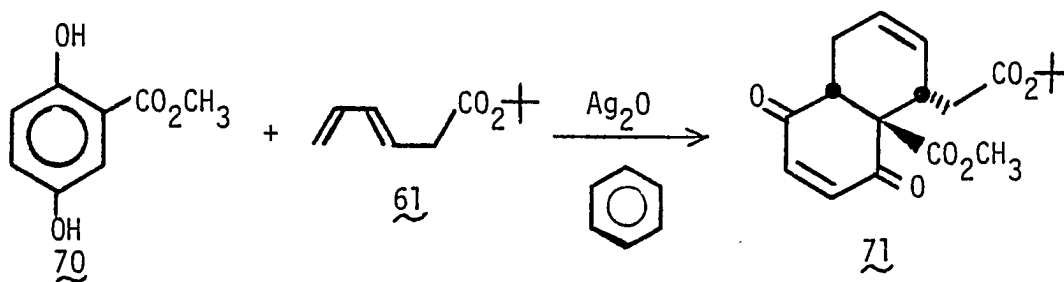


known to be a potent dienophile (45), but was also known to be unstable to light, air and water (46). It had been prepared in moderate yield by the oxidation of methyl gentisate 70 with silver oxide (46). The

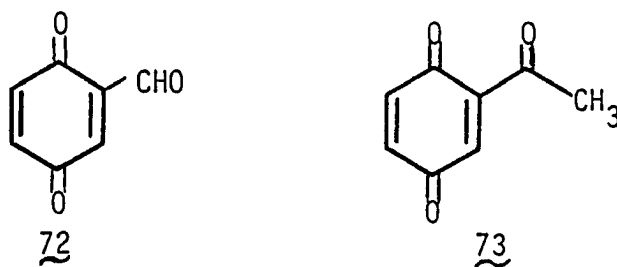


required oxidation proved to be more difficult than originally expected. The yields were disgustingly low and the product was recrystallized from a solvent more disgusting than the yields, carbon disulfide. The main reason for the low yields must have been the instability of the quinone. It seemed reasonable that the yields could be increased if there were some way to trap the quinone as it was formed. Bearing in mind the reactivity of 69 in the Diels-Alder reaction, it seemed only natural to attempt to trap the quinone with a suitably functionalized diene.

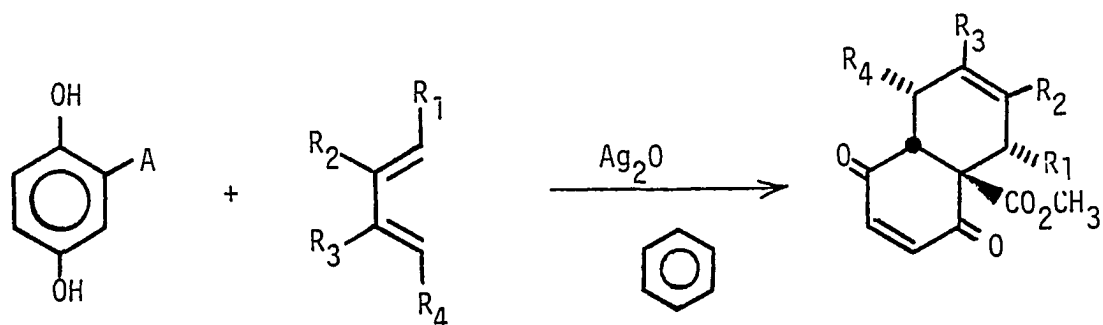
To test the hypothesis of utilizing a one-pot technique wherein the diene, the requisite hydroquinone, and silver oxide are stirred in the absence of light to afford the Diels-Alder adducts, diene 59, hydroquinone 70, and silver oxide were stirred in a benzene solution overnight (47). The reaction produced the desired adduct 71 in quantitative yield.



With this promising result, the reaction was tested for its generality. Diels-Alder reactions of aldehyde 72 and ketone 73 have

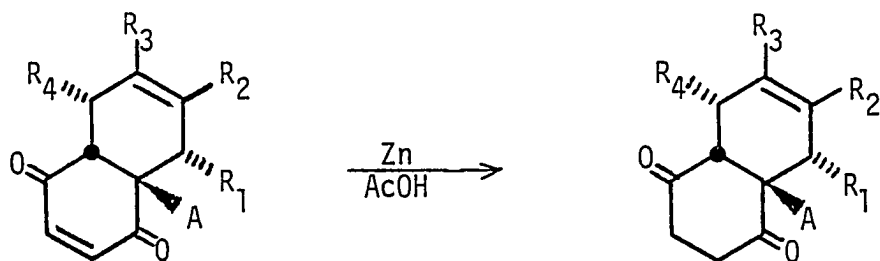


not been reported. A number of dienes were reacted with the in situ generated quinones 69, 72 and 73 (48). The results of the reaction are shown below.



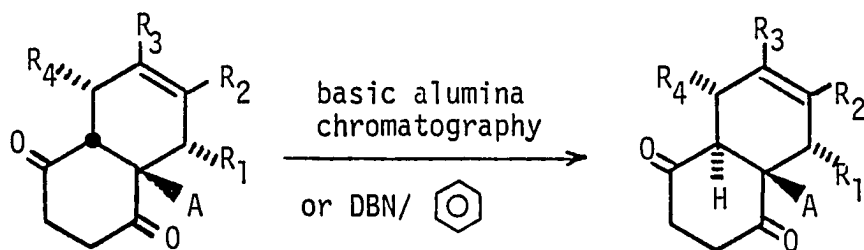
A	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	compound	% yield
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CO <sub>2</sub> <u>t</u> -Bu	H	H	H	<u>71</u>	100
CO <sub>2</sub> CH <sub>3</sub>	OSiMe <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	<u>74</u>	96
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> Ph	CH <sub>3</sub>	H	H	<u>75</u>	95
CO <sub>2</sub> CH <sub>3</sub>	H	(H)(CH <sub>3</sub> )	(CH <sub>3</sub> )(H)	H	<u>76</u>	100
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OSiMe <sub>2</sub> <u>t</u> -Bu	CH <sub>3</sub>	H	H	<u>77</u>	98
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OH	CH <sub>3</sub>	H	H	<u>78</u>	97
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OSiMe <sub>3</sub>	CH <sub>3</sub>	H	H	<u>79</u>	95
CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CO <sub>2</sub> Et	CH <sub>3</sub>	H	H	<u>80</u>	100
CHO	CH <sub>2</sub> CO <sub>2</sub> Et	CH <sub>3</sub>	H	H	<u>81</u>	94
CHO	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> Ph	CH <sub>3</sub>	H	H	<u>82</u>	97
COCH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> Ph	CH <sub>3</sub>	H	H	<u>83</u>	100
COCH <sub>3</sub>	OAc	H	CH <sub>3</sub>	H	<u>84</u>	100

The Diels-Alder adducts were easily reduced with zinc and acetic acid. The reaction was quick and provided the diketones in excellent yields.



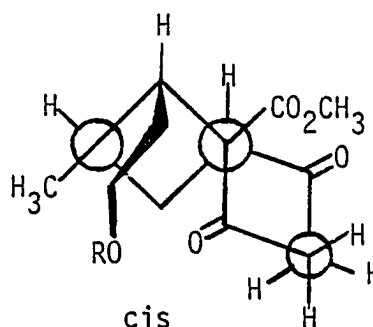
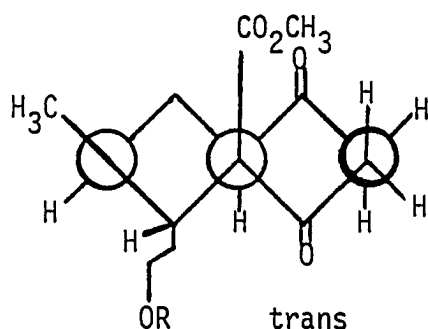
<u>Diels-Alder adduct</u>	<u>diketone</u>	<u>% yield</u>
<u>71</u>	<u>85</u>	100
<u>74</u>	<u>86</u>	98
<u>75</u>	<u>87</u>	96
<u>76</u>	<u>88</u>	100
<u>77</u>	<u>89</u>	95
<u>78</u>	<u>90</u>	92
<u>80</u>	<u>91</u>	96
<u>82</u>	<u>92</u>	91
<u>83</u>	<u>93</u>	93
<u>84</u>	<u>94</u>	95

Epimerization of hydrogen at the ring junction of the diketones was accomplished by chromatography on basic alumina (49) or more conveniently with a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). There was an upfield shift of approximately 0.10 ppm in the



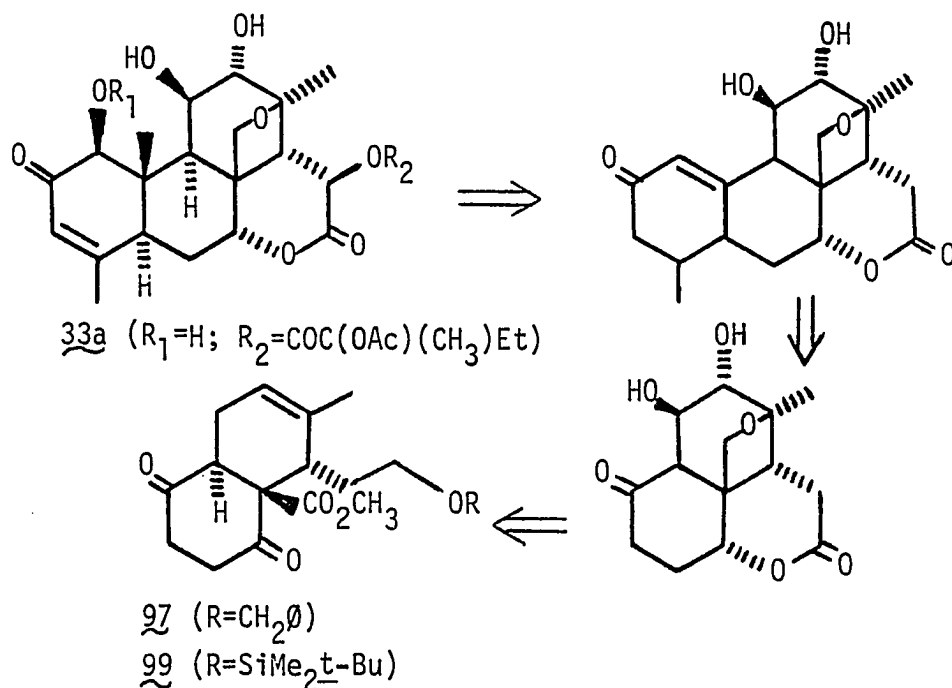
<u>cis-diketone</u>	<u>trans-diketone</u>	<u>% yield</u>
<u>85</u>	<u>95</u>	70
<u>86</u>	<u>96</u>	90
<u>87</u>	<u>97</u>	79
<u>88</u>	<u>98</u>	95
<u>89</u>	<u>99</u>	88
<u>91</u>	<u>100</u>	65

chemical shift of the carbomethoxy protons in going from the cis-fused esters to the trans-fused esters. This parallels observations made by Ansell, et al. (45b) and Goldsmith, et al. (45d) in related systems. In the cis configuration, the molecule is flexible and the methoxy portion of the carbomethoxy group can sweep through the anisotropic shielding cone of the C-4-carbonyl group. This allows the methoxy group to experience both positive and negative shielding. On the other hand, in the trans-fused system, which is more rigid, the methoxy group will, on the average, reside in the positive shielding cone and result in a net shift to higher field.

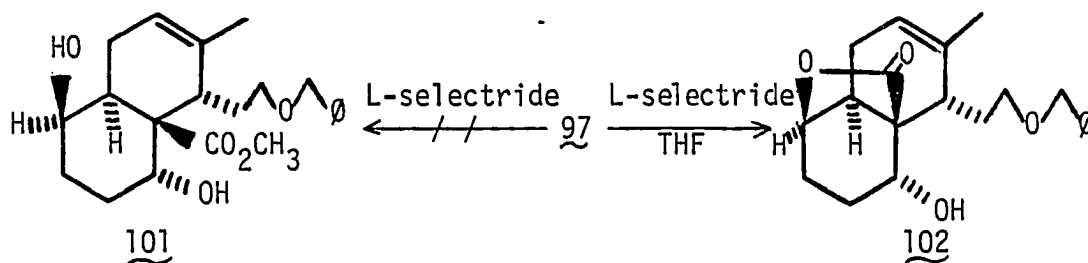


## Approach to the Quassinoids Revisited

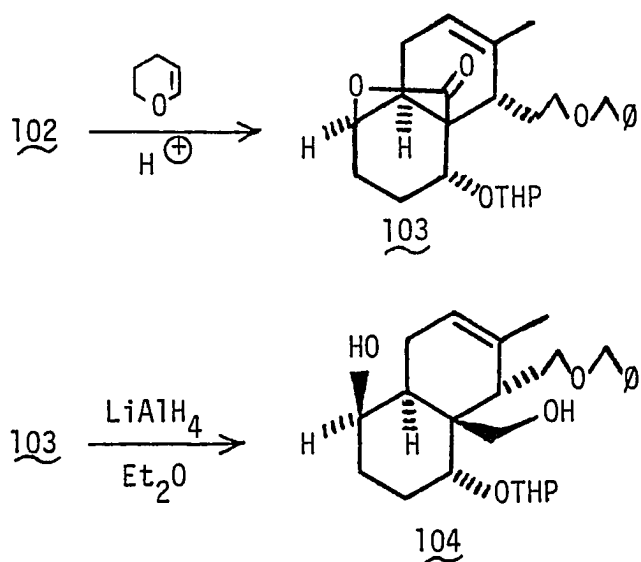
Retrosynthetic analysis showed the trans-diketones (i.e., 97 + 99) to be ideal for the construction of quassinoids such as quasimarin 33a.



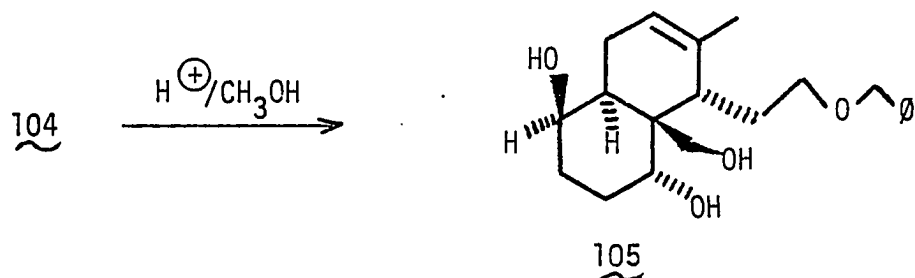
Diketone 97 was reduced with L-selectride (49) in the hope of obtaining the diaxial diol 101. Brown and Krishnamurthy (49) have demonstrated the preference for equatorial delivery of the hydride by this reagent. Instead of the diol, the lactone alcohol 102 was produced. This was not surprising in view of the proximity of the alkoxide produced from the reduction to the carbomethoxy group.



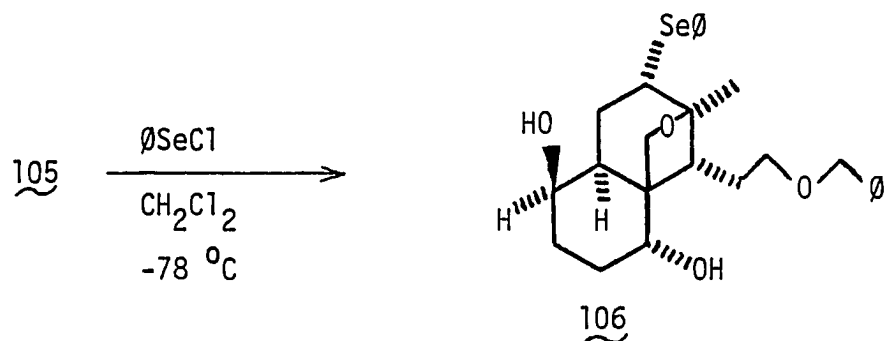
Attempts were made to reduce the lactone 102 to the triol 105 directly using lithium aluminum hydride. Some of the desired triol 105 was obtained, but the yield was low and the product was always contaminated by some unidentifiable impurity. This was presumably due to base catalyzed fragmentation of the  $\beta$ -hydroxy ester moiety. An indirect route involving protection, reduction and deprotection proved to be more satisfactory. Protection of the alcohol with dihydropyran according to the method of Miyashita, et al. (50) yielded the tetrahydropyranyl ether (THP) 103. The lactone was reduced with lithium aluminum hydride to provide diol 104 in 99% yield.



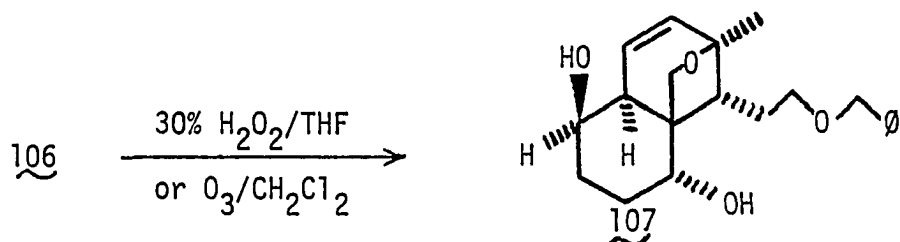
Removal of the THP protecting group (50) provided the triol 105 in 99% overall yield from lactone 102.



The E ring was constructed by utilization of the phenylselenoetherification procedure developed by Nicolaou, et al. (51). Reaction of triol 105 with phenylselenenyl chloride in methylene chloride at  $-78^\circ\text{C}$  produced the selenoether 106 in 83% yield.

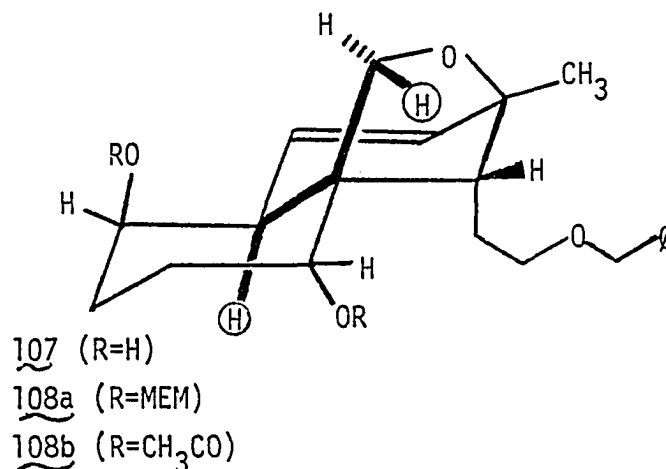


Oxidative elimination of the phenylselenenyl group using 30% hydrogen peroxide (51) yielded allylic ether 107. This oxidation was more conveniently run on large scale using ozone (52) instead of 30% hydrogen peroxide.





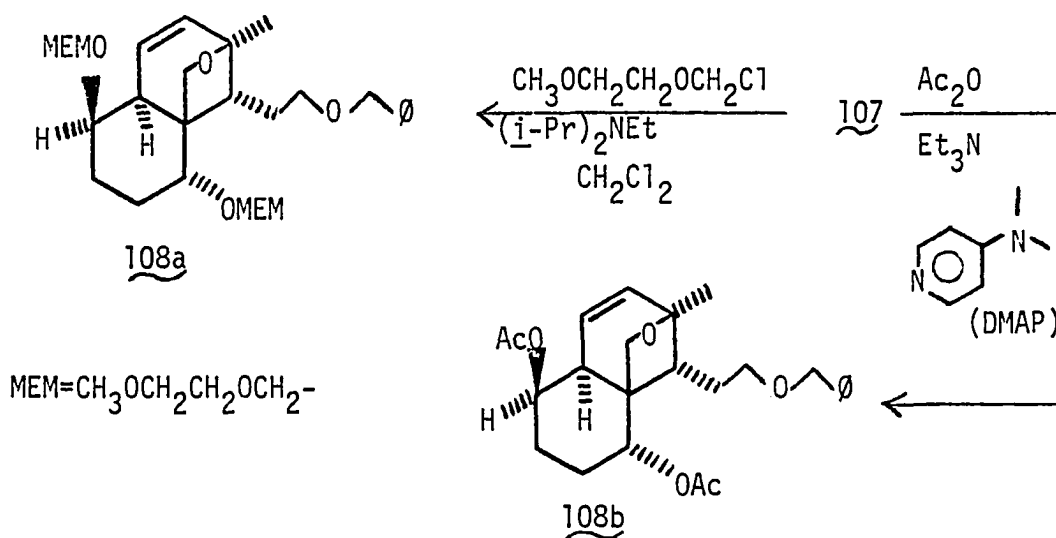
Allylic ether 107 exhibited a five hydrogen singlet at  $\delta$  7.32, a two-hydrogen singlet at  $\delta$  5.64, a two-hydrogen singlet at  $\delta$  4.54, and a three hydrogen singlet at  $\delta$  1.30 for the phenyl group, the olefin, the benzyl ether, and the methyl group, respectively. The most interesting feature of the NMR spectrum was the nonequivalence of the hydrogens of the newly formed tetrahydrofuran ring. The hydrogen, which is syn to



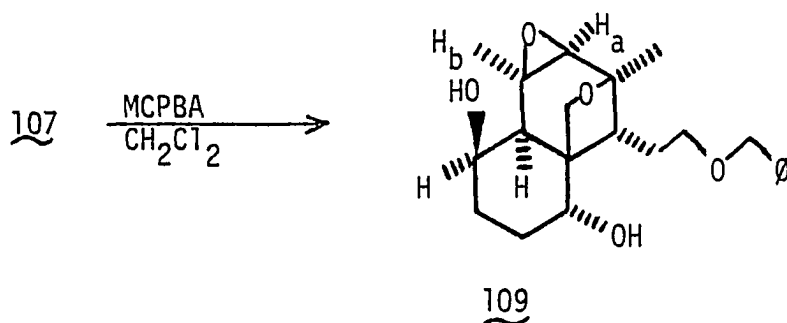
the olefin, appeared as a doublet ( $J = 8$  Hz) at  $\delta$  4.68. The anti hydrogen appeared as a doublet of doublets ( $J = 8$  and 2 Hz) at  $\delta$  3.96. The additional coupling is due to the "W-conformation" (53) of the four sigma bonds between the two circled hydrogens (see 107 above).

Diol 107 could be protected as the dimethoxyethoxymethyl (MEM) ether (54) 108a or the diacetate 108b (55).

Attempts to epoxidize olefin 108a led only to the recovery of starting material. This was undoubtedly due to the congested steric environment around the double bond. It was found that the olefin could only be epoxidized with the aid of the axial homoallylic alcohol.



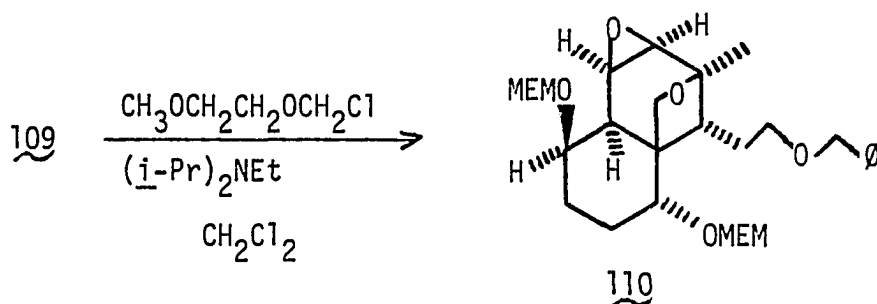
Reaction of diol 107 with *m*-chloroperoxybenzoic acid produced epoxide 109. It was anticipated that the presence of the homoallylic alcohol would direct the epoxidation. This was realized by the obtention of epoxide 109 with stereochemistry as shown below. Examination of



Dreiding models revealed the dihedral angle between  $\text{H}_b$  and the hydrogen at the ring junction to be approximately  $44^\circ$  for the  $\beta$ -epoxide. The expected coupling constant for such an angle is 3-8 Hz (53), which is in good agreement with the observed coupling of 3 Hz. This value was obtained by irradiation of  $\text{H}_a$  (see 109), which appeared as a doublet

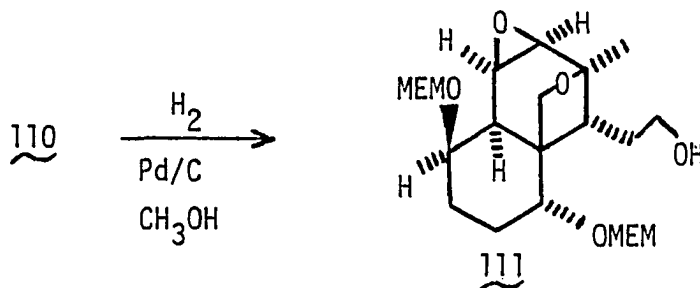
( $J = 4$  Hz) at  $\delta$  2.88. The doublet of doublets ( $J = 3$  and 4 Hz) centered at  $\delta$  3.22, for  $H_b$ , collapsed to a doublet ( $J = 3$  Hz). The  $\alpha$ -epoxide would have had a dihedral angle close to  $90^\circ$ , which would have resulted in little or no coupling between the two hydrogens.

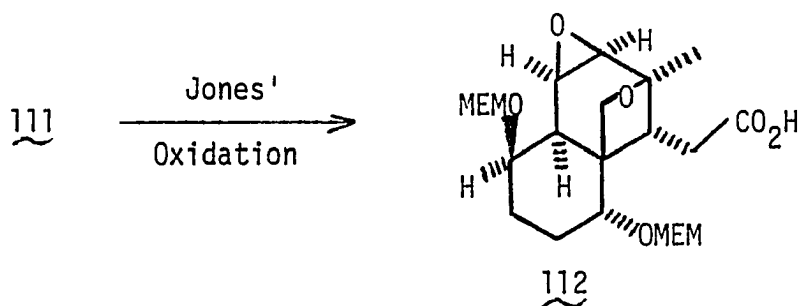
Before attempting to open the epoxide, diol 109 was protected as the di-MEM ether 110. All attempts to open the epoxide to the trans-



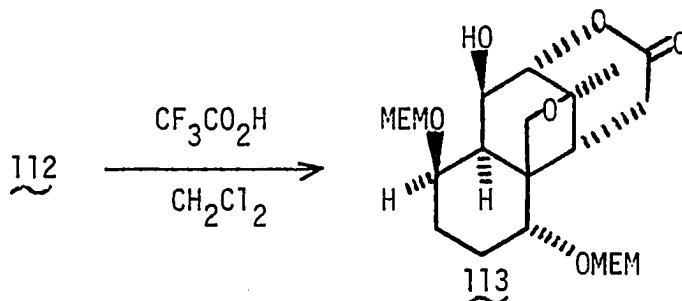
diaxial diol with a variety of external nucleophiles (see Experimental), in accord with the work of Dailey and Fuchs (38), met with failure. Rather than employ their strategy, it was decided to convert the benzyl ether protected alcohol to a carboxylic acid and utilize it as an internal nucleophile.

Hydrogenolysis of benzyl ether 110 with 10% Pd/C in methanol produced alcohol 111 in 97% yield. Oxidation of the alcohol to the acid was accomplished using Jones' oxidation (56).



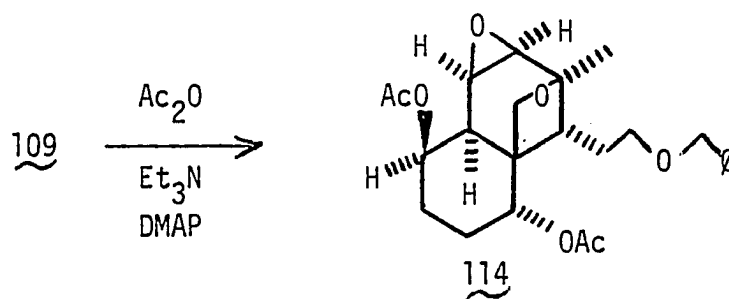


The acid 112 on treatment with trifluoroacetic acid cyclized to hydroxy lactone 113. The alcohol 113, however, could not be protected under a variety of conditions.

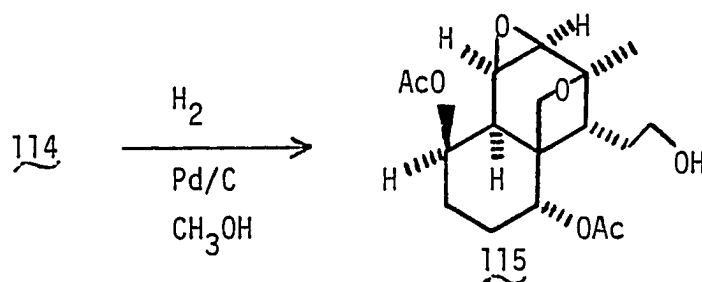


The problem of opening the epoxide seemed to be solved; it was now just a matter of altering the protective groups. Perhaps the MEM-group was causing additional steric problems than were already inherent in the molecule itself. It was decided to opt for the acetate as a protecting group, hoping to remove some of the 1,3-diaxial interactions.

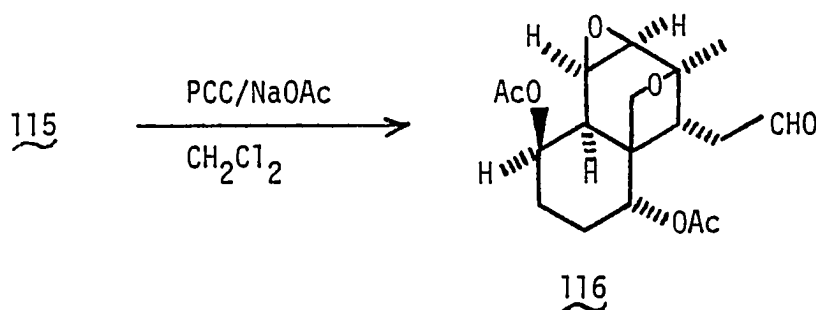
Just as with 108a, attempts to epoxidize 108b led to the recovery of starting material. It was obvious the homoallylic alcohol was necessary for the epoxidation. Acetylation of diol 109 employing conditions similar to those for the transformation of diol 107 to the diacetate 108b afforded diacetate 114.



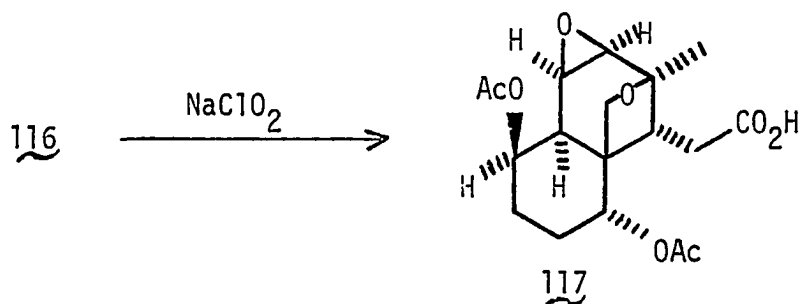
Hydrogenolysis of benzyl ether 114 with 10% Pd/C in methanol produced alcohol 115 in 98% yield. Oxidation of alcohol 115 to carboxylic



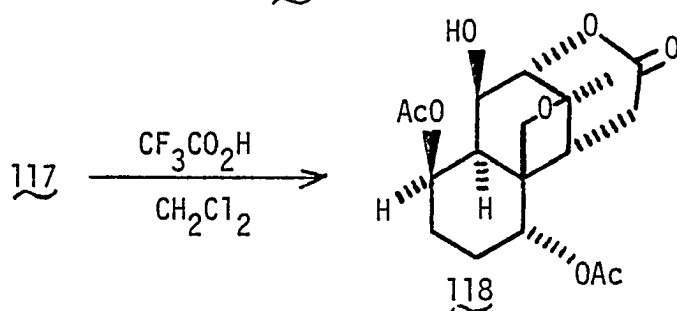
acid 117 was most effectively accomplished utilizing a two-step procedure. Alcohol 115 was first oxidized with pyridinium chlorochromate (PCC) (57) to aldehyde 116.



Conversion of aldehyde 116 to acid 117 was achieved using sodium chlorite (58).



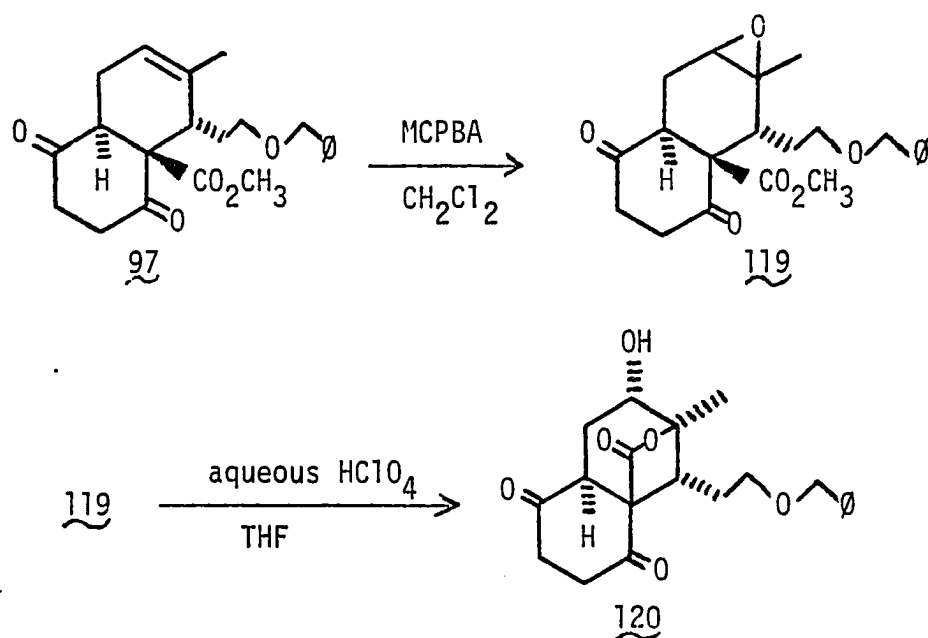
Reaction of epoxide 117 with trifluoroacetic acid in methylene chloride afforded lactone 118.



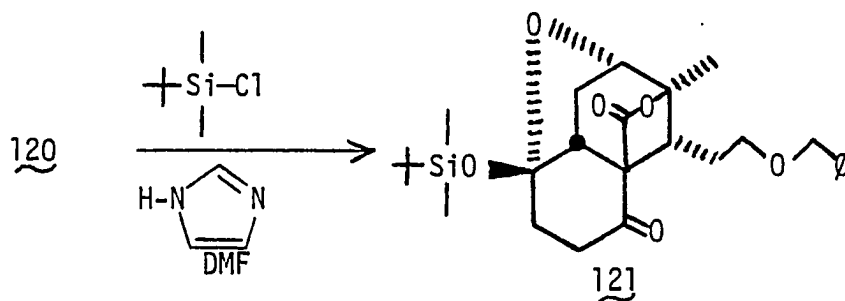
The alcohol 118 could not be selectively protected under a number of conditions. Even the highly reactive silyl perchlorates (59) would not react with the alcohol. The environment of the  $\beta$ -face of the molecule must be too congested to allow any reaction at the desired center.

In the advent of these results, the possibility of selectively generating the ketone necessary for the annelation sequence seemed bleak. It was therefore decided to employ an alternative strategy.

The new approach began with the diketone 97. Treatment of 97 with *m*-chloroperoxybenzoic acid afforded the epoxide 119. Reaction of epoxide 119 with aqueous perchloric acid in tetrahydrofuran (60) yielded the lactone alcohol 120. Treating alcohol



**120** with *t*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethyl formamide (**61**) did not silylate the alcohol, but instead led to the ketal **121**. The structure for **121** was not postulated until examination

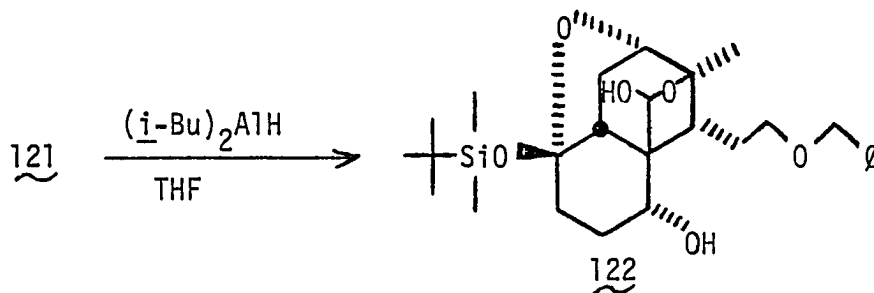


of the  $^{13}\text{C}$  NMR spectrum revealed the disappearance of one of the ketone carbons and the appearance of a ketal carbon at 105.283 ppm.

This was a very fortuitous turn of events. The reaction not only protected the alcohol, but also the ketone which is necessary for the annelation scheme. The ring junction also had to be epimerized

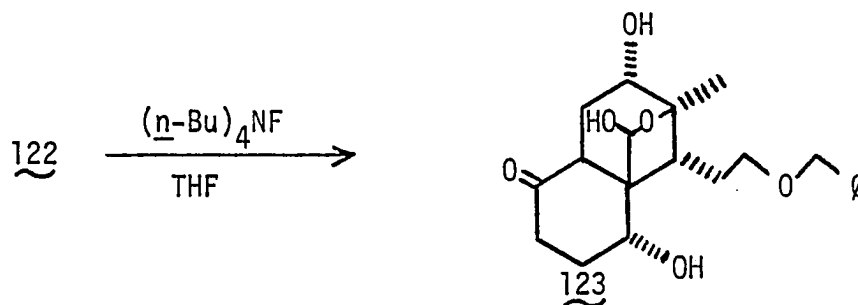
to form a cis-decalin system in order to accommodate the newly formed five-membered ring.

The functiodifferentiated 1,4-diketone 121 was treated with diisobutylaluminum hydride (62) to produce the lactol alcohol 122.



The stereochemistry of the alcohol should be as shown due to the concave nature of the cis-decalin system. The bulky reducing reagent should deliver the hydride from the  $\beta$ -face of molecule producing the  $\alpha$ -alcohol in accord with previous work (40).

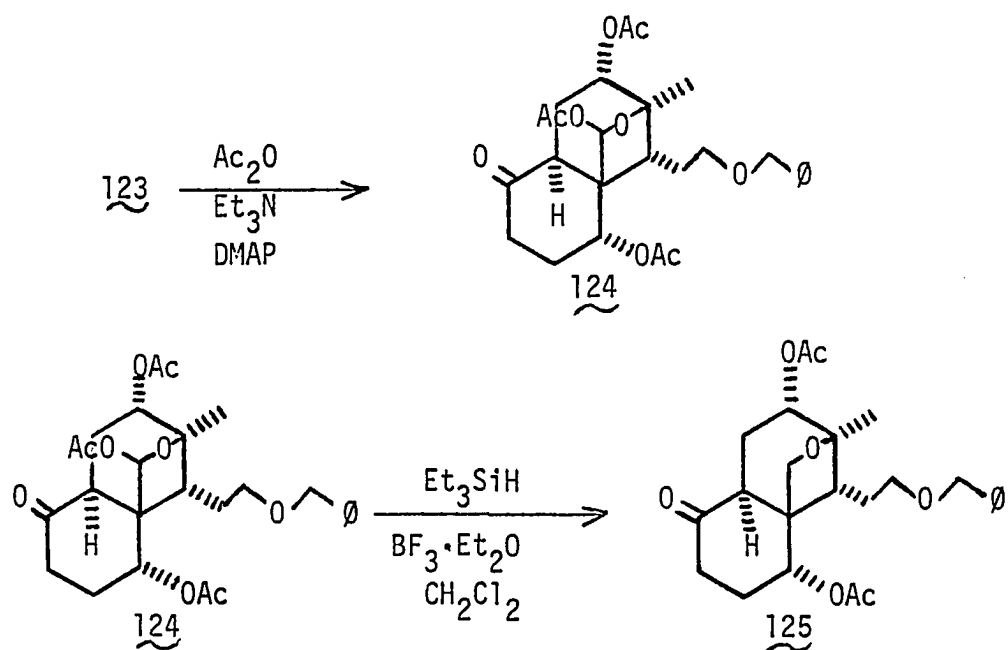
The internal ketal was unraveled to yield the highly crystalline lactol diol 123 using tetra-n-butylammonium fluoride (61). Treatment



of 123 with excess acetic anhydride, triethylamine, and N,N-dimethyl aminopyridine produced triacetate 124. The acetoxylactol was reduced to the ether by utilizing triethylsilane and boron trifluoride etherate.

Compound 125 contains six of the asymmetric centers present in quasimarin. It also possesses suitable functionality for further





elaboration of the A- and D-rings. It should therefore serve as an useful intermediate for the final construction of quasimarin.

## EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR 4250 or Acculab 2 spectrometer. The NMR spectra were recorded using a Varian EM-360, A-60 or HA-100 spectrometer or a Hitachi-Perkin Elmer R20-B spectrometer. All chemical shifts are reported in  $\delta$  relative to tetramethylsilane as an internal standard. The  $^{13}\text{C}$  spectra were recorded using a Jeol FX-90Q. The chemical shifts for  $^{13}\text{C}$  are reported in ppm relative to the central peak of  $\text{CDCl}_3$  (77.06 ppm). An AEI-MS902 mass spectrometer was used for mass spectral data. Ultraviolet spectra were recorded on a Cary-14 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Tetrahydrofuran was distilled from  $\text{LiAlH}_4$  prior to use.

Preparation of 4-(2-Furyl)-2-Methyl-1,3-Butadiene (12)

To a suspension of 1.97 g (5.5 mmol) of (methyl)-triphenylphosphonium bromide in THF at  $-40^\circ\text{C}$  was added a 1 M THF solution of 5.5 mmol of LDA (63). The reaction was allowed to slowly warm to  $0^\circ\text{C}$  and stirred at  $0^\circ\text{C}$  until all the salt had dissolved. The reaction was cooled to  $-40^\circ\text{C}$ . A THF solution (2 M) of 4-(2-furyl)-3-buten-2-one (.68 g, 5 mmol) was added dropwise over 2 minutes. The reaction was allowed to slowly warm to room temperature and stir for 10 hours. The reaction was diluted with an equal volume of hexane and filtered through a column of Florisil (25 g) using hexane as the eluent. Concentration of the organic solution yielded .56 g (4.18 mmol, 84%) of 12. NMR ( $\text{CCl}_4$ ) 1.94 (br s, 3H), 5.15 (m, 2H), 6.20 (m, 1H), 6.28 (d, 1H,  $J = 8$  Hz), 6.30 (m, 1H), 6.88 (d, 1H,  $J = 8$  Hz), 7.40 (m, 1H). IR (film)  $\text{cm}^{-1}$ ,

3120, 1615, 955, 880. High resolution mass spectrum for  $C_9H_{17}O$  requires 134.07317, measured 134.07168.

Preparation of 2-Dimethyl t-Butyl Silyloxy 1,3,5,7-Nonatetraene (13)

To a solution of a 1:1 LDA:HMPA complex (64) (11 mmoles) in 15 mL of THF at  $-78^{\circ}C$  was added a 2 M THF solution of 1.36 g (10 mmoles) of 3,5,7-nonatriene-2-one. The reaction was stirred at  $-78^{\circ}C$  for 20 minutes. A 2 M THF solution of 1.806 g (12 mmoles) t-butyl dimethyl silyl chloride was added and the reaction allowed to stir at room temperature for 3 hours. The reaction was poured into 100 mL of hexane and washed with  $H_2O$  and brine. The organic solution was dried ( $Na_2SO_4$ ), filtered and concentrated in vacuo. Yield 2.5 g (100%) of 13. NMR ( $CCl_4$ ) 0.2 (s, 6H), 1.02 (s, 9H), 1.8 (d, 3H), 4.30 (br s, 2H), 5.72-6.50 (envelope, 6H). High resolution mass spectrum for  $C_{15}H_{26}OSi$  requires m/e 250.17530, measured m/e 250.17492.

General Procedure for Enynones 14, 15 and 16

The copper acetylides were prepared according to the method of Castro, et al. (65). To a stirred suspension of 10 mmoles copper acetylide and 10 mmoles of LiI in 20 mL of ether was added 10 mmoles of the appropriate acid chloride. The reaction was stirred at room temperature for 2 hours. To the reaction was added 5 mL of HMPA. The reaction was allowed to stir at room temperature overnight. It was then poured into 50 mL of hexane and washed with 5 M HCl and brine. The organic solution was dried ( $Na_2SO_4$ ), filtered and concentrated. The residue was chromatographed on silica gel using hexane/ether as the solvent.

1-Phenyl-4-penten-1-yn-3-one (14)

Yield 1.40 g (90%). NMR ( $\text{CCl}_4$ ) 6.18 (m, 1H), 6.54 (m, 2H), 7.5 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 2196, 1640, 1603. High resolution mass spectrum for  $\text{C}_{11}\text{H}_8\text{O}$  requires 156.05752, measured 156.0558.

4-Methyl-1-phenyl-4-penten-1-yn-3-one (15)

Yield 1.45 g (85%), mp  $56^\circ\text{C}$  (recrystallized from hexane). NMR ( $\text{CCl}_4$ ) 1.97 (br s, 3H), 6.05 (m, 1H), 6.54 (m, 1H), 7.5 (m, 5H). IR ( $\text{CCl}_4$ )  $\text{cm}^{-1}$ , 2200, 1645. High resolution mass spectrum for  $\text{C}_{12}\text{H}_{10}\text{O}$  requires  $m/e$  170.07317, measured  $m/e$  170.07041.

Ethyl 4-oxo-5-hexen-2-ynoate (15)

Yield .91 g (60%). NMR ( $\text{CCl}_4$ ) 1.38 (t, 3H,  $J = 3.8$  Hz), 4.35 (q, 2H,  $J = 3.8$  Hz), 6.25 (m, 1H), 6.55 (m, 2H). IR (film)  $\text{cm}^{-1}$ , 2140, 1720, 1660. High resolution mass spectrum for  $\text{C}_8\text{H}_8\text{O}_3$  requires  $m/e$  152.04735, measured  $m/e$  152.04510.

## General Procedure for Monocycloaddition Products

A 0.5 M  $\text{CCl}_4$  solution of 2 mmoles of the appropriate bis-diene and 2 mmoles of the appropriate bis-dienophile was refluxed under nitrogen. The progress of the reaction was followed by NMR. When the reaction was judged complete, the reaction was concentrated and the residue chromatographed on silica gel using hexane/ether as the solvent.

1-(2-(1,3-Pentadienyl)-4-*t*-butyl dimethyl silyloxy cyclohex-3-enyl)-3-phenyl-propyn-1-one (23a)

Yield 0.45 g (55%). NMR ( $\text{CCl}_4$ ) 0.20 (s, 6H), 1.0 (s, 9H), 1.78

(d, 3H), 4.88 (m, 1H), 5.6-6.2 (envelope, 4H), 7.55 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 2980, 2200, 1665.

1-(2-(1,3-Pentadienyl)-1-methyl-4-*t*-butyl dimethyl silyloxy cyclohex-3-enyl)-3 phenyl-propyn-1-one (23b)

Yield 0.42 g (50%). NMR ( $\text{CCl}_4$ ) 0.20 (s, 6H), 1.0 (s, 9H), 1.18 (br s, 3H), 1.80 (d, 3H), 4.90 (m, 1H), 5.60-6.20 (envelope, 4H), 7.55 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 2980, 2200, 1660.

Methyl 6-(1,3-pentadienyl)-2-(propen-1-one)-4-*t*-butyl dimethyl silyloxy-3,6 dihydrobenzoate (25)

Yield 0.346 g (50%). NMR ( $\text{CCl}_4$ ) 0.20 (s, 9H), 1.85 (d, 3H), 6.1-6.6 (acryloyl pattern, 3H).

2, 4a, 4b, 7-Tetrahydro-7-methyl-3-*t*-butyl dimethyl silyloxy-9H-fluoren-9-one (26)

Yield 0.22 g (34%). NMR ( $\text{CCl}_4$ ) 0.20 (s, 6H), 1.0 (s, 9H), 4.80 (m, 1H), 6.30 (m, 2H), 6.90 (m, 2H).

1-(2-(2-Furyl)-4-methyl-cyclohex-3-enyl)-3-phenyl-propyn-1-one (28a)

Yield 0.20 g (35%). NMR ( $\text{CCl}_4$ ) 1.74 (br s, 3H), 5.50 (m, 1H), 5.95 (m, 1H), 6.15 (m, 1H), 7.4 (m, 6H). IR (film)  $\text{cm}^{-1}$ , 2200, 1665.

1-(2-(2-Furyl)-1,4 dimethyl-cyclohex-3-enyl)-3-phenyl-propyn-1-one (28b)

Yield 0.22 g (37%). NMR ( $\text{CCl}_4$ ) 1.35 (s, 3H), 1.77 (br s, 3H), 5.40 (m, 1H), 5.95 (m, 1H), 6.15 (m, 1H), 7.4 (m, 6H). IR (film)  $\text{cm}^{-1}$ , 2200, 1665. High resolution mass spectrum for  $\text{C}_{21}\text{H}_{20}\text{O}_2$  requires 304.14633, measured 304.14456.

## General Procedure for Second Cycloaddition

The appropriate monocycloaddition product was dissolved in enough toluene to make the solution  $\sim 0.10$  M. The solution was degassed by bubbling Argon through for  $\sim 5$  minutes. The solution was heated in a sealed tube at  $240^\circ\text{C}$  for 3-5 hours. The solution was concentrated and the residue chromatographed on silica gel using ether/hexane as the solvent.

1, 2, 4a, 4b, 7, 8, 8a, 9a-Octahydro-7, 8-dimethyl-3, 9H-fluoren-3, 9 dione (22a)

Yield 0.16 g (35% overall). NMR ( $\text{CDCl}_3$ )  $\delta$  1.1-1.35 (m, 6H), 2.0-3.1 (m, 12H), 5.6-5.9 (br s, 2H). IR (film)  $\text{cm}^{-1}$ , 1720, 1745.

1, 2, 4a, 4b, 7, 8, 8a, 9a-Octahydro-7-methyl-8-phenyl-3-t-butyl-dimethyl silyloxy-9H-fluoren-9-one (22b)

Yield 0.26 g (32% overall). NMR ( $\text{CCl}_4$ ) 0.20 (s, 6H), 0.70 (d, 3H), 1.0 (s, 9H), 5.05 (m, 1H), 5.20 (m, 2H), 7.5 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 1735. High resolution mass spectrum for  $\text{C}_{26}\text{H}_{36}\text{O}_2\text{Si}$  requires 408.24847, measured 408.24856.

1, 2, 4a, 4b, 7, 9a-Hexahydro-7-methyl-8-phenyl-3-t-butyl-dimethyl silyloxy-9H-fluoren-9-one (24a)

Yield 0.24 g (30% overall). NMR ( $\text{CCl}_4$ ) 0.2 (s, 6H), 1.0 (s, 9H), 5.1 (m, 1H), 5.85 (m, 1H), 6.0 (m, 1H), 7.4 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 1720. High resolution mass spectrum for  $\text{C}_{26}\text{H}_{34}\text{O}_2\text{Si}$  requires 406.23281, measured 406.23270.

1, 2, 4a, 4b, 7, 9a-Hexahydro-7, 9a-dimethyl-8-phenyl-3-t-butyl-dimethyl silyloxy-9H-fluoren-9-one (24b)

Yield 0.235 g (28% overall). NMR ( $\text{CCl}_4$ ) 0.20 (s, 6H), 1.0 (s, 9H), 5.0 (m, 1H), 5.90 (m, 1H), 6.05 (m, 1H), 7.50 (m, 5H). IR (film)  $\text{cm}^{-1}$ , 1720. High resolution mass spectrum for  $\text{C}_{27}\text{H}_{36}\text{O}_2\text{Si}$  requires 420.24846, measured 420.24838.

7-Methyl-3-t-butyl Dimethyl Silyloxy-9H-fluoren-9-one (27)

To a stirred solution of 22 mg of (26) in 2 mL of toluene was added 30 mg of DDQ. The reaction was refluxed for 24 hours. The solution was diluted with ether, filtered and concentrated. Yield .21 g (100%). NMR ( $\text{CDCl}_3$ ) 0.28 (s, 6H), 1.02 (s, 9H), 2.36 (s, 3H), 7.45 (m, 6H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 1700. High resolution mass spectrum for  $\text{C}_{20}\text{H}_{24}\text{O}_2\text{Si}$  requires 324.15456, measured 324.15114. UV (MeOH) 245,278 nm.

Preparation of 1-(2,4-hexadienyloxy) Butadiene (59)

To a stirred 1 M solution of 1.42 g (10 mmoles) of 1-trimethylsilyloxy butadiene at 0 °C was added 10 mmoles of n-butyl lithium over a period of 5 minutes. The reaction was warmed to room temperature and stirred for 15 minutes. The reaction was cooled to -78 °C and 1.305 g (10 mmoles) of sorbyl chloride in 3 mL of THF was added dropwise over 3 minutes. The reaction was stirred at -78 °C for 5 minutes. It was then allowed to slowly warm to 0 °C. The reaction was poured into 75 mL of ether and washed with  $\text{H}_2\text{O}$ , saturated  $\text{NaHCO}_3$ , and brine. The ether was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The

residue was recrystallized from hexane. It yielded 0.68 g (4.1 mmol) of yellow needles with a melting point of 59 °C. NMR (CDCl<sub>3</sub>) 1.90 (d, 3H,  $J = 6$  Hz), 5.15 (m, 2H), 6.10 (m, 5H), 7.30 (m, 2H). IR (CCl<sub>4</sub>) cm<sup>-1</sup>, 3090, 3030, 2960, 2940, 1700, 1650, 1620, 1325, 1240, 1135, 995. High resolution mass spectrum for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> requires 164.08373, measured 164.08346.

#### Preparation of 1-(3,5-Hexadienyloxy) Butadiene (56)

To a stirred solution of a 1:1 LDA:HMPA complex (2.2 mmol) in 2 mL of THF at -78 °C was added a 2 M THF solution of 0.328 g (2 mmol) of 59 over 2 minutes. The reaction was stirred at -78 °C for 20 minutes. The reaction was quenched at -78 °C with 0.264 g (4.4 mmol) of acetic acid and allowed to warm to room temperature. The solution was poured into 50 mL of pentane and washed with H<sub>2</sub>O, saturated NaHCO<sub>3</sub>, and brine. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to yield 0.30 g (1.83 mmol) of 56. NMR (CDCl<sub>3</sub>) 3.20 (d, 2H,  $J = 7$  Hz), 5.20 (m, 4H), 6.20 (m, 5H), 7.50 (d, 1H,  $J = 12$  Hz). IR (film) cm<sup>-1</sup>, 3100, 3040, 2970, 2940, 1730, 1650, 1620, 1330, 1240, 1140, 995, 920. High resolution mass spectrum for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> requires 164.08373, measured 164.0836.

#### Attempted Reactions of 56 and Ethyl Propiolate (57)

A 0.5 M CCl<sub>4</sub> solution of 0.392 g (4 mmol) of ethyl propiolate and 0.60 g (3.7 mmol) of 56 was refluxed for 72 hours. Examination of the NMR spectrum showed no indication of any addition. NMR (CCl<sub>4</sub>) 3.0



(s, 1H, acetylenic hydrogen), 3.20 (d, 2H,  $\underline{J} = 7$  Hz,  $\overset{\text{O}}{\parallel}\text{-CH}_2\text{-CH=C}$ ), and 7.50 (d, 1H,  $\underline{J} = 12$  Hz,  $\text{-O-CH=C-}$ ).

A 0.5 M toluene solution of 0.196 g (2 mmol) of ethyl propiolate and 0.30 g (1.85 mmol) of 56 was refluxed for 48 hours. The reaction was monitored by thin layer chromatography (TLC) and NMR. Both methods indicated the bis-diene 56 had decomposed.

A 0.5 M toluene solution of the two reactants was heated in a sealed tube at 240 °C for 4 hours. Once again the bis-diene had disappeared and the ethyl propiolate remained unchanged.

A 1.0 M  $\text{CH}_2\text{Cl}_2$  solution of 0.155 g (1.58 mmol) of 57 was cooled to -78 °C. To this solution was added 0.082 g (0.32 mmol) of  $\text{SnCl}_4$ . The reaction was stirred at -78 °C for 20 minutes. Then a 1.0 M  $\text{CH}_2\text{Cl}_2$  solution of 56 was added over a period of 2 minutes. The reaction was allowed to slowly warm to 0 °C. It was then poured into 30 mL of ether and washed with saturated  $\text{NaHCO}_3$  and brine. The ether was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. There was no indication of an addition product. There was, however, partial destruction of bis-diene 56.

#### Preparation of Dimethyl Phthalate (60)

A 0.5 M acetic anhydride solution of 0.26 g (1.83 mmol) of dimethylacetylenedicarboxylate and 0.30 g (1.83 mmol) of 56 was refluxed for 12 hours. The reaction was poured into 30 mL of ether and washed with water, saturated  $\text{NaHCO}_3$ , and brine. The ether was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to yield 0.20 g of

dimethyl phthalate, identical in all respects with an authentic sample. NMR ( $\text{CDCl}_3$ )  $\delta$  3.30 (s, 3H), 7.60 (m, 2H). IR (film)  $\text{cm}^{-1}$ , 3030, 2960, 1725, 1615, 1590, 1440, 1290, 1190, 1125, 1075, 1040, 960.

#### Preparation of t-Butyl-3,5-hexadienoate (61)

To a 1.0 M THF solution of 1:1 LDA:HMPA complex (82.5 mmoles) at  $-78^\circ\text{C}$  was added a 2.0 M THF solution of 12.6 g (75 mmoles) of t-butyl sorbate. The reaction was stirred at  $-78^\circ\text{C}$  for 20 minutes. The reaction was then quenched with 9.90 g (165 mmoles) of acetic acid and allowed to warm to room temperature. The reaction was poured into 250 mL of ether and washed with water, saturated  $\text{NaHCO}_3$ , and brine. The ether was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The residue was distilled at reduced pressure. Collecting the fraction that boiled at  $56^\circ\text{C}/5\text{ mm}$  yielded 8.80 g (52.4 mmoles) of 61. NMR ( $\text{CDCl}_3$ )  $\delta$  1.45 (s, 9H), 3.0 (d, 2H,  $J = 6\text{ Hz}$ ), 5.10 (m, 2H), 5.60-6.20 (m, 3H). IR (film)  $\text{cm}^{-1}$ , 3090, 2990, 2940, 1735, 1395, 1370, 1255, 1160, 1000, 950, 900. High resolution mass spectrum for  $\text{C}_{10}\text{H}_{16}\text{O}_2$  requires 168.11503, measured 168.11505. 90 MHz C-13 NMR ( $\text{CDCl}_3$ )  $\delta$  28.032, 39.139, 80.581, 116.282, 126.304, 133.889, 136.543, 170.565.

#### Preparation of 1,4-Dihydro-2,3-dicarbomethoxyphenylacetic

##### Acid t-Butyl Ester (62)

To a 1.0 M benzene solution of 1.68 g (10 mmoles) of t-butyl-3,5-hexadienoate 61 was added 2.13 g (15 mmoles) of dimethyl acetylenedicarboxylate. The solution was refluxed for 12 hours and concentrated in vacuo. The residue was chromatographed on silica gel (10/1 weight ratio)

using ethyl acetate/hexane as the solvent. This resulted in 2.44 g (7.87 mmol) of 62. NMR ( $\text{CDCl}_3$ ) 1.45 (s, 9H), 2.40 (m, 3H), 2.97 (m, 2H), 3.80 (s, 6H), 5.82 (br s, 2H). IR (film)  $\text{cm}^{-1}$ , 2980, 2960, 1725, 1640, 1435, 1370, 1265, 1150, 1070.

Preparation of 1,4-Dihydro-2,3-dicarbomethoxyphenylacetic Acid (63)

To a stirred 0.5 M  $\text{CCl}_4$  solution of 0.62 g (2.0 mmol) of 62 was added 0.44 g (2.2 mmol) of trimethylsilyl iodide. The reaction was stirred at room temperature for 20 minutes. The reaction was monitored by NMR by watching the shift of the t-butyl peak at  $\delta$  1.45 to  $\delta$  1.98. The reaction was poured into 10 mL of  $\text{CH}_2\text{Cl}_2$ . To the  $\text{CH}_2\text{Cl}_2$  solution was added 3 mL of  $\text{H}_2\text{O}$ . The water layer was made basic (pH  $\sim$  10) with 10% NaOH. The separatory funnel was shaken well. Then the pH of the water was checked. The 10% NaOH was added and the reaction shaken until the aqueous layer remained basic (pH  $\sim$  10). Extract the reaction once with  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was acidified (pH  $\sim$  3) with 6 N HCl. The aqueous layer was then extracted three times with 25 mL portions of  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  was dried over  $\text{Na}_2\text{SO}_4$  with a few crystals of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  added, filtered and concentrated in vacuo to yield 0.38 g (1.50 mmol) of 1,4-dihydro-2,3-dicarbomethoxyphenylacetic acid (63). NMR ( $\text{CDCl}_3$ ) 2.60 (m, 3H), 3.0 (m, 2H), 3.87 (s, 6H), 5.85 (d,  $J$  = 2 Hz). IR (film)  $\text{cm}^{-1}$ , 3500-2400, 1730-1670, 1640, 1430, 1250, 1185, 1055, 1000, 900, 710.

## Preparation of 1,4-Dihydro-2,3-dicarbomethoxyphenylacetic

Acid Chloride (64)

To a 0.3 M  $\text{CHCl}_3$  solution of 0.38 g (1.5 mmol) of 63 was added 0.196 g (1.65 mmol)  $\text{SOCl}_2$ . The reaction was stirred at room temperature for 12 hours. The  $\text{CHCl}_3$  was removed and the residue placed on the pump to remove last traces of HCl and unreacted  $\text{SOCl}_2$  to yield 0.41 g (1.5 mmol) of 64. NMR ( $\text{CDCl}_3$ ) 0.31 (m, 5H), 3.80 (s, 6H), 5.90 (s, 2H). IR (film)  $\text{cm}^{-1}$ , 3040, 3000, 2960, 1795, 1720, 1675, 1640, 1430, 1265, 1190, 1155, 1140, 1060, 1000, 960, 890.

## Preparation of 1-(1,4-Dihydro-2,3-dicarbomethoxyphenylacetoxy)

Butadiene (65)

The reaction conditions were identical to the ones used for the preparation of 59 (*vide supra*), except the reaction was scaled down for 0.41 g (1.5 mmol) of 64. The reaction yielded 0.40 g (1.30 mmol) of 65. NMR ( $\text{CDCl}_3$ ) 2.60 (m, 3H), 3.0 (m, 2H), 3.80 (s, 6H), 5.20 (m, 2H), 5.85 (br s, 2H), 6.15 (m, 2H), 7.50 (d, 1H,  $J = 12$  Hz). IR (film)  $\text{cm}^{-1}$ , 3100, 3060, 3020, 2970, 1760-1720, 1670, 1440, 1280, 1150, 1060, 1000.

## Thermolyses of 1-(1,4-Dihydro-2,3-dicarbomethoxyphenylacetoxy)

Butadiene (65)

A 0.10 M *o*-dichlorobenzene solution containing 0.153 g (0.5 mmol) of 65 was refluxed for 12 hours. Removal of the solvent yielded as the only recognizable product, dimethyl phthalate.

A 0.10 M o-dichlorobenzene solution containing 0.153 g (0.5 mmoles) of 65 was heated in a sealed tube for 2 hours at 220 °C. Removal of the solvent yielded dimethyl phthalate.

A 0.10 M xylene solution of 0.153 g (0.5 mmoles) of 65 was passed through a vertical 300-cm vicor column packed with quartz chips. The column was heated to 650 °C and placed under a vacuum of 25 mm. The xylene solution passed through in 0.10 mL portions at 2 minute intervals. The product was trapped in flask at -78 °C. When the addition was complete, the collection flask was warmed to room temperature. Removal of the xylene yielded dimethyl phthalate.

#### Preparation of 1,4-Dihydro-2-carboethoxyphenylacetic

##### Acid t-Butyl Ester (66)

A 1.0 M toluene solution containing 2.35 g (14 mmoles) of 59 and 1.764 g (18 mmoles) of ethyl propiolate was refluxed for 40 hours. The toluene was removed and the residue chromatographed on silica gel (10/1, w/w) using hexane/ethyl acetate as solvent. The reaction produced 2.10 g (7.9 mmoles) of 66. NMR (CDCl<sub>3</sub>) 1.30 (t, 3H, J = 8 Hz), 1.43 (s, 9H), 2.36 (m, 2H), 2.87 (m, 3H), 4.25 (q, 2H, J = 8 Hz), 5.81 (br s, 2H), 7.0 (m, 1H). IR (film) cm<sup>-1</sup>, 3040, 2980, 2940, 1730-1700, 1390, 1370, 1250, 1195, 1150, 1090, 1060.

#### Preparation of 1,4-Dihydro-2-carboethoxyphenylacetic Acid

To a 0.5 M methylene chloride solution of 1.40 g (5.3 mmoles) of 66 was added 1.21 g (10.6 mmoles) of trifluoroacetic acid. The reaction was stirred at room temperature for 8 hours. The reaction was poured

into 5 mL of H<sub>2</sub>O and extracted three times with 25 mL portions of methylene chloride. The combined methylene chloride extractions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to yield 0.86 g (4.1 mmol) of 1,4-dihydro-2-carboethoxyphenylacetic acid. NMR (CDCl<sub>3</sub>) 1.33 (t, 3H,  $J$  = 8 Hz), 2.56 (m, 2H), 2.90 (m, 3H), 4.30 (q, 2H,  $J$  = 8 Hz), 5.88 (br s, 2H), 7.19 (t, 1H,  $J$  = 4 Hz). IR (film) cm<sup>-1</sup>, 3600-2600, 3040, 2995, 1750-1690, 1635, 1420, 1255, 1200, 1100, 1060, 720.

#### Preparation of 1,4-Dihydro-2-carboethoxyphenylacetic Acid Chloride (67)

To a 0.5 M chloroform solution containing 0.161 g (0.76 mmol) of 1,4-dihydro-2-carboethoxyphenylacetic acid was added 0.131 g (1.1 mmol) of thionyl chloride. The reaction was stirred at room temperature for 12 hours. The solvent was removed and residue *kügelrohr*ed at 1 mm with an oven temperature of 150 °C to yield 0.157 g (0.69 mmol) of 67. NMR (CDCl<sub>3</sub>) 1.30 (t, 3H,  $J$  = 8 Hz), 2.80-3.20 (m, 5H), 4.24 (q, 2H,  $J$  = 8 Hz), 5.83 (br s, 2H), 7.18 (t, 1H,  $J$  = 4 Hz). IR (film) cm<sup>-1</sup>, 3040, 2995, 2940, 2905, 1800, 1730-1700, 1680, 1640, 1400, 1300, 1250, 1090, 1060, 960, 710. High resolution mass spectrum for C<sub>10</sub>H<sub>13</sub>ClO<sub>3</sub> requires 228.055327, measured 228.05525.

#### Preparation of 1-(1,4-Dihydro-2-carboethoxyphenylacetoxy)

##### Butadiene (68)

The reaction conditions were identical to the ones used for the preparation of 59 (vide supra), except the reaction was scaled down for 0.2285 g (1 mmol) of 67. The reaction yielded 0.257 g (0.98 mmol)

of 68. NMR ( $\text{CDCl}_3$ ) 1.30 (t, 3H,  $J = 8$  Hz), 2.55 (m, 2H), 2.83 (m, 3H), 4.23 (q, 2H,  $J = 8$  Hz), 5.20 (m, 2H), 5.80 (br s, 2H), 6.13 (m, 2H), 7.10 (m, 1H), 7.47 (d, 1H,  $J = 12$  Hz). IR (film)  $\text{cm}^{-1}$ , 3100, 2040, 2990, 2980, 2970, 1750, 1710, 1675, 1660, 1250, 1140, 1090, 1050, 990, 920, 910.

#### Attempted Cyclizations of 68

A 0.10 M xylene solution containing 0.257 g (0.98 mmoles) of 68 was refluxed for 16 hours. Removal of the solvent yielded a product which was no longer 68, but showed no signs of cyclization.

A 0.10 M benzene solution containing 0.131 g (0.5 mmoles) of 68 was heated in a sealed tube for 2 hours at  $240^\circ\text{C}$ . Removal of the benzene yielded starting material.

To a 0.10 M methylene chloride solution of 0.131 g (0.5 mmoles) of 68 at  $-78^\circ\text{C}$  was added 0.20 mL of a 1.0 M methylene chloride solution of  $\text{SnCl}_4$ . The reaction was allowed to slowly warm to  $0^\circ\text{C}$ . To the solution was added 2 mL of saturated  $\text{NaHCO}_3$ . The reaction was stirred vigorously for 5 minutes. The reaction was then extracted twice with 25 mL portions of methylene chloride. The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to yield an unidentifiable mixture of compounds.

A 0.10 M benzene solution of 0.131 g (0.5 mmoles) of 68 was subjected to flow pyrolysis similar to those employed in the thermolysis of 62. Removal of the solvent yielded an intractable tar.

## Preparation of Ethyl-4-methyl-2,4-hexadienoate

A 0.5 M methylene chloride solution containing 13.61 g (162 mmol) of tiglic aldehyde and 56.4 g (162 mmol) of carboethoxymethylenetriphenylphosphorane was refluxed for 24 hours. The reaction was concentrated. To the residue was added 300 mL of hexane. The triphenylphosphine oxide which precipitated was filtered and washed with hexane. The precipitate was leached once more with hexane. The combined hexane solutions were cooled to  $-20^{\circ}\text{C}$  and any solid which separated was filtered. The hexane was removed to yield 21.45 g (139 mmol) of ethyl-4-methyl-2,4-hexadienoate. NMR ( $\text{CDCl}_3$ ) 1.28 (t, 3H,  $J = 8$  Hz), 1.79 (s, 3H), 1.82 (d, 3H,  $J = 7.5$  Hz), 4.20 (q, 2H,  $J = 8$  Hz), 5.74 (d, 1H,  $J = 16$  Hz), 6.02 (q, 1H,  $J = 7.5$  Hz), 7.31 (d, 1H,  $J = 16$  Hz). IR (film)  $\text{cm}^{-1}$ , 3020, 2980, 2940, 1710, 1630, 1620, 1440, 1390, 1360, 1260, 1220, 1165, 1030, 980, 815. Bp  $82^{\circ}\text{C}/5$  mm Hg.

## Preparation of Ethyl-4-methyl-3,5-hexadienoate

The reaction conditions were similar to those employed for the preparation of 6 except the reaction was scaled up for 21.47 g (139.4 mmol) of ethyl-4-methyl-2,4-hexadienoate. The reaction yielded 16.90 g (110 mmol) of ethyl-4-methyl-3,5-hexadienoate, bp  $65^{\circ}\text{C}/4$  mm Hg. NMR ( $\text{CDCl}_3$ ) 1.26 (t, 3H,  $J = 8$  Hz), 1.76 (br s, 3H), 3.18 (d, 2H,  $J = 8$  Hz), 4.14 (q, 2H,  $J = 8$  Hz), 5.0 (d, 1H,  $J = 11$  Hz), 5.14 (d, 1H,  $J = 18$  Hz), 5.66 (t, 1H,  $J = 8$  Hz), 6.4 (dd, 1H,  $J = 11$  and 18 Hz). 90 MHz  $\text{C}-13$  NMR ( $\text{CDCl}_3$ ) 11.837, 14.112, 33.993, 60.537, 111.948, 123.379, 136.814, 140.715, 171.431. IR (film)  $\text{cm}^{-1}$ , 3095, 3040, 3005,



2980, 2940, 2880, 1730, 1640, 1605, 1375, 1250, 1155, 1000, 950. High resolution mass spectrum for  $C_9H_{14}O_2$  requires 154.09938, measured 154.09777.

#### Preparation of 4-Methyl-3,5-hexadien-1-ol

A 1.0 M ether solution of 15.4 g (100 mmoles) of ethyl-4-methyl-3,5-hexadienoate was added dropwise to a stirred 0.5 M ether suspension of 3.8 g (100 mmoles) of lithium aluminum hydride at such rate as to maintain a gentle reflux. The reaction was stirred overnight at room temperature. The reaction was successively treated with 3.8 mL of  $H_2O$ , added dropwise carefully, 3.8 mL of 15% NaOH, and 11.4 mL of  $H_2O$ . The reaction was stirred until the precipitate became fine and granular. The precipitate was filtered and washed with ether. Removal of the ether yielded 11.0 g (98 mmoles) of 4-methyl-3,5-hexadien-1-ol. NMR ( $CDCl_3$ ) 1.78 (s, 3H), 2.42 (q, 2H,  $J = 7$  Hz), 3.66 (t, 2H,  $J = 7$  Hz), 4.96 (d, 1H,  $J = 11$  Hz), 5.12 (d, 1H,  $J = 18$  Hz), 5.50 (t, 1H,  $J = 7$  Hz), 6.39 (dd, 1H,  $J = 11$  and 18 Hz). 90 MHz C-13 NMR ( $CDCl_3$ ) 11.729, 31.771, 61.999, 111.081, 128.200, 136.381, 141.202. IR (film)  $cm^{-1}$ , 3400-3300, 3090, 3040, 3000, 2985, 2930, 2885, 1640, 1600, 1440, 1410, 1385, 1045, 985, 890. High resolution mass spectrum for  $C_7H_{12}O$  requires 112.08882, measured 112.08881.

#### Preparation of 4-Methyl-3,5-hexadienyl Benzyl Ether

A 4.0 M THF solution of 11.0 g (98 mmoles) of 4-methyl-3,5-hexadien-1-ol was added dropwise over a period of 15 minutes to a stirred suspension of 2.83 g (118 mmoles) of mineral oil free NaH in 200 mL of

THF. The reaction was stirred at room temperature for 2 hours. It was then cooled to 0 °C and 16.76 g (98 mmol) of benzyl bromide in 25 mL of THF was added over a period of 10 minutes. The reaction was allowed to warm to room temperature and stir for 12 hours. The reaction was filtered. The precipitate was washed with hexane. The organic solution was diluted with an equal volume of hexane and washed with H<sub>2</sub>O and brine. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was distilled at reduced pressure collecting the material at 65 °C/1 mm Hg. The reaction yielded 14.85 g (73.5 mmol) of 4-methyl-3,5-hexadienyl benzyl ether. NMR (CDCl<sub>3</sub>) 1.74 (s, 3H), 2.46 (q, 2H, J = 8 Hz), 3.50 (t, 2H, J = 8 Hz), 4.50 (s, 2H), 4.94 (d, 1H, J = 11 Hz), 5.10 (d, 1H, J = 18 Hz), 5.51 (t, 2H, J = 8 Hz), 6.38 (dd, 1H, J = 11 and 18 Hz), 7.30 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 11.729, 29.007, 69.638, 72.888, 110.810, 127.442, 127.550, 128.309, 128.688, 135.622, 138.602, 141.365. IR (film) cm<sup>-1</sup>, 3080, 3060, 3030, 3000, 2980, 2920, 2855, 1640, 1600, 1490, 1450, 1355, 1100, 985, 890, 730, 690. High resolution mass spectrum for C<sub>14</sub>H<sub>18</sub>O requires 202.13577, measured 202.13595.

#### Preparation of 4-Methyl-3,5-hexadienyl t-Butyl Dimethylsilyl Ether

To a 2.0 M DMF solution of 8.40 g (75 mmol) of 4-methyl-3,5-hexadien-1-ol was added 11.22 g (165 mmol) of imidazole. This was followed by addition of 13.56 g (90 mmol) of t-butyl dimethylsilyl chloride. The reaction was stirred at 35 °C for 10 hours. The DMF solution was poured into 5 volumes of H<sub>2</sub>O and the solution exhaustively extracted with hexane. The hexane was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and

concentrated in vacuo. The residue was distilled at reduced pressure to provide 14.80 g (65.48 mmol) of 4-methyl-3,5-hexadienyl *t*-butyl dimethylsilyl ether, bp 57 °C/1 mm Hg. NMR (CDCl<sub>3</sub>) 0.20 (s, 6H), 0.89 (s, 9H), 1.76 (br s, 3H), 2.40 (q, 2H,  $J = 7.5$  Hz), 3.62 (t, 2H,  $J = 7.5$  Hz), 4.94 (d, 1H,  $J = 11$  Hz), 5.08 (d, 1H,  $J = 18$  Hz), 5.48 (t, 1H,  $J = 7.5$  Hz), 6.38 (dd, 1H,  $J = 11$  and 18 Hz). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 0.00, 11.770, 25.903, 31.992, 62.038, 110.810, 128.695, 135.716, 141.440. IR (film) cm<sup>-1</sup>, 3095, 3020, 2960, 2900, 2860, 1640, 1605, 1380, 1250, 1095, 985, 930, 835.

#### Preparation of 4-Methyl-3,5-hexadienyl Trimethylsilyl Ether

To a 0.5 M ether solution of 16.0 g (143 mmol) of 4-methyl-3,5-hexadien-1-ol and 16.97 g (215 mmol) of pyridine was added 23.35 g (215 mmol) of trimethylsilyl chloride dropwise over 20 minutes. The reaction was stirred at room temperature for 4 hours. The reaction was filtered and the precipitate washed with ether. The ether was washed with water, 1 N HCl, saturated NaHCO<sub>3</sub>, and brine. The ether was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was distilled at reduced pressure to afford 17.7 g (96.2 mmol) of the trimethylsilyl ether, bp 41 °C/1 mm Hg. NMR (CDCl<sub>3</sub>) 0.20 (s, 9H), 1.76 (br s, 3H), 2.40 (q, 2H,  $J = 7.5$  Hz), 3.62 (t, 2H,  $J = 7.5$  Hz), 4.94 (d, 1H,  $J = 11$  Hz), 5.08 (d, 1H,  $J = 18$  Hz), 5.48 (t, 1H,  $J = 7.5$  Hz), 6.38 (dd, 1H,  $J = 11$  and 18 Hz). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 0.00, 11.771, 31.995, 62.037, 110.811, 128.694, 135.718, 141.440. IR (film) cm<sup>-1</sup>, 3100, 3020, 2960, 2905, 2870, 1640, 1610, 1415, 1380, 1250, 1095, 985, 930, 835, 740.

### General Procedure for In Situ Diels-Alder Reactions

A 0.5 M benzene solution containing equimolar amounts of the appropriate diene and hydroquinone were placed in a dry, wide-mouth, amber bottle. After the reaction was cooled to ca. 10 °C, two molar equivalents of silver oxide were added all at once to the stirred solution. The reaction was then allowed to stir overnight at room temperature. The reaction was diluted with ether and filtered. The silver was washed with additional ether. Concentration of the solution produced the Diels-Alder adducts in high yield.

#### 4a- $\beta$ -Carbomethoxy-5 $\alpha$ -(acetic acid *t*-butyl ester)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (71)

Compound 71 was produced in 100% yield on a 25 mmole scale. NMR (CDCl<sub>3</sub>) 1.45 (s, 9H), 2.35 (m, 3H), 2.60 (d, 2H,  $\underline{J}$  = 7.5 Hz), 3.15 (m, 1H), 3.52 (t, 2H,  $\underline{J}$  = 7.5 Hz), 3.77 (s, 3H), 5.65 (br s, 2H), 6.54 (d, 1H,  $\underline{J}$  = 10.5 Hz), 6.78 (d, 1H,  $\underline{J}$  = 10.5 Hz). IR (film) cm<sup>-1</sup>, 3040, 2995, 2980, 1750-1680, 1600, 1440, 1370, 1340, 1260-1210, 1155, 910, 840.

#### 4a- $\beta$ -Carbomethoxy-6, 8 $\alpha$ -dimethyl-5 $\alpha$ -trimethylsilyloxy-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (74)

The reaction was performed on a 5 mmole scale to yield 74 in 96%. NMR (CDCl<sub>3</sub>) 1.44 (d, 3H,  $\underline{J}$  = 8 Hz), 1.77 (br s, 3H), 2.20 (envelope, 1H), 3.63 (d, 1H,  $\underline{J}$  = 5 Hz), 3.76 (s, 3H), 4.64 (s, 1H), 5.38 (br s, 1H), 6.53 (d, 1H,  $\underline{J}$  = 10 Hz), 6.77 (d, 1H,  $\underline{J}$  = 10 Hz). IR (film) cm<sup>-1</sup>, 3040, 3005, 2970, 1750, 1715, 1685, 1445, 1250, 1100, 1060, 1040, 910, 845,

755. High resolution mass spectrum for  $C_{17}H_{24}O_5Si$  requires 336.13931, measured 336.13979.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (75)

The reaction yielded 75 in 95% yield on a 100 mmole scale. NMR ( $CDCl_3$ ) 1.52 (m, 2H), 1.74 (br s, 3H), 2.15 (envelope, 1H), 2.78 (m, 1H), 2.92 (m, 1H), 3.28 (t, 2H,  $J = 6$  Hz), 3.70 (s, 1H), 3.78 (m, 1H), 4.37 (s, 2H), 5.24 (m, 1H), 6.58 (d, 1H,  $J = 11$  Hz), 6.74 (d, 1H,  $J = 11$  Hz), 7.24 (s, 5H). 90 MHz C-13 NMR ( $CDCl_3$ ) 20.989, 23.210, 31.174, 41.631, 46.507, 53.006, 64.708, 68.717, 72.780, 118.936, 127.550, 128.200, 136.489, 138.060, 139.848, 140.552, 170.240, 196.027, 197.544. IR (film)  $cm^{-1}$ , 3085, 3040, 3030, 2950, 2920, 2860, 1740, 1720, 1680, 1600, 1490, 1460, 1445, 1430, 1360, 1230, 1090, 1025, 840, 795, 730, 690. High resolution mass spectrum for  $C_{22}H_{24}O_5$  requires 368.16238, measured 368.16243. Recrystallized from benzene/hexane, mp 75-6 °C.

4a- $\beta$ -Carbomethoxy-7-methyl-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (76)

This product was produced in quantitative yield on a 5 mmole scale. The compound is actually a 70/30 mixture of the regioisomers of the methyl group at C-6 and C-7, with the expected C-7 isomer being the 70% of the mixture. NMR ( $CDCl_3$ ) 1.68 (br s, 3H), 2.10-2.40 (envelope, 2H), 2.56 (m, 2H), 3.64 (t, 1H,  $J = 7$  Hz), 3.76 (s, 3H), 5.38 (m, 1H), 6.66 (s, 2H). 90 MHz C-13 NMR ( $CDCl_3$ ) 22.940, 28.303, 28.411, 32.422,

48.076, 48.835, 53.060, 59.833, 117.636, 117.961, 131.397, 137.897, 139.414, 170.456, 194.943, 197.489. IR (film)  $\text{cm}^{-1}$ , 3060, 3020, 2960, 2900, 2840, 1730, 1700, 1680, 1600, 1435, 1250, 1160, 1100, 1065, 800. High resolution mass spectrum for  $\text{C}_{13}\text{H}_{14}\text{O}_4$  requires 234.08921, measured 234.09010.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-ethyl *t*-butyl dimethylsilyl ether)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (77)

Compound 77 was prepared in 94% yield on a 25 mmole scale.

300 MHz NMR (courtesy of Tom Lyttle, Instrument Services, Iowa State University) ( $\text{CDCl}_3$ ). The peaks from the *t*-butyl dimethylsilyl group have been eliminated for clarity. NMR ( $\text{CDCl}_3$ ) 1.44 (m, 2H), 1.75 (m, 3H), 2.02-2.23 (envelope, 1H), 2.88-3.00 (m, 2H), 3.44 (t, 2H,  $J = 7$  Hz), 3.75 (s, 3H), 3.82 (dd, 1H,  $J = 3.8$  and 10 Hz), 5.28 (m, 1H), 6.73 (d, 1H,  $J = 11$  Hz), 6.86 (d, 1H,  $J = 11$  Hz). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 0.027, 18.443, 23.427, 23.915, 26.028, 36.647, 39.193, 44.177, 53.223, 62.270, 67.200, 119.424, 137.572, 138.385, 142.123, 168.614, 193.643, 197.273. IR (film)  $\text{cm}^{-1}$ , 2960, 2930, 2860, 1745, 1730, 1690, 1470, 1430, 1250, 1220, 1090, 830, 770.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-hydroxyethyl)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (78)

On a 72 mmole scale, compound 78 was produced in 97% yield. NMR ( $\text{CDCl}_3$ ) 1.53 (t, 2H,  $J = 7.5$  Hz), 1.76 (br s, 3H), 2.15-2.40 (envelope, 1H), 2.80-3.10 (m, 2H), 3.30 (t, 2H,  $J = 7.5$  Hz), 3.75 (s, 3H), 3.90 (m, 1H), 5.30 (m, 1H), 6.70 (d, 1H,  $J = 10.5$  Hz), 6.90 (d, 1H,  $J = 10.5$

Hz). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 20.989, 21.748, 23.265, 34.047, 41.523, 46.561, 52.464, 53.169, 61.350, 64.762, 119.099, 136.543, 139.956, 140.823, 170.348, 196.298, 197.706. IR (film) cm<sup>-1</sup>, 3600-3200, 3095, 3040, 2960, 2880, 1725, 1690, 1670, 1600, 1475, 1430, 1235, 1025, 830, 790, 670.

4a-β-Carbomethoxy-6-methyl-5α-(2-ethyl trimethylsilyl ether)-4a, 5, 8, 8a-β-tetrahydronaphthalene-1,4-dione (79)

Compound 79 was obtained in 95% yield on a 100 mmole scale. NMR (CDCl<sub>3</sub>) 0.20 (s, 9H), 1.54 (m, 2H), 1.76 (br s, 3H), 2.20 (envelope, 1H), 2.90 (m, 2H), 3.45 (t, 2H, J = 7 Hz), 3.74 (s, 3H), 3.82 (dd, 1H, J = 4 and 10 Hz), 5.28 (m, 1H), 6.66 (d, 1H, J = 11 Hz), 6.82 (d, 1H, J = 11 Hz). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 0.063, 21.198, 23.150, 34.141, 41.424, 46.820, 52.934, 61.388, 64.834, 118.744, 136.823, 140.010, 140.595, 170.379, 196.001, 197.497. IR (film) cm<sup>-1</sup>, 3090, 2960, 2880, 1740, 1730, 1685, 1470, 1250, 1090, 830, 770.

4a-β-Carbomethoxy-6-methyl-5α-(acetic acid ethyl ester)-4a, 5, 8, 8a-β-tetrahydronaphthalene-1,4-dione (80)

Compound 80 was prepared in 100% yield on a 30 mmole scale. NMR (CDCl<sub>3</sub>) 1.21 (t, 3H, J = 8 Hz), 1.75 (br s, 3H), 2.50 (m, 5H), 3.40 (m, 1H), 3.79 (s, 3H), 4.12 (q, 2H, J = 8 Hz), 5.37 (m, 1H), 6.73 (s, 2H). IR (film) cm<sup>-1</sup>, 3040, 2960, 2920, 1730, 1690, 1600, 1440, 1250, 1080, 800, 770.

4a- $\beta$ -Formyl-6-methyl-5 $\alpha$ -(acetic acid ethyl ester)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (81)

On a 5 mmole scale, compound 81 was obtained in 94% yield. NMR ( $\text{CDCl}_3$ ) 1.22 (t, 3H,  $J$  = 8 Hz), 1.74 (br s, 3H), 2.25 (m, 3H), 2.75 (m, 2H), 3.72 (dd, 1H,  $J$  = 3 and 9 Hz), 4.10 (q, 2H,  $J$  = 8 Hz), 5.40 (m, 1H), 6.54 (d, 1H,  $J$  = 10.5 Hz), 6.85 (d, 1H,  $J$  = 10.5 Hz), 9.58 (s, 1H). IR (film)  $\text{cm}^{-1}$ , 3040, 2940, 2920, 2860, 1730, 1700, 1670, 1455, 1250, 1090, 800.

4a- $\beta$ -Formyl-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (82)

Compound 82 was produced in 97% yield on a 5 mmole scale. NMR ( $\text{CDCl}_3$ ) 1.50 (m, 2H), 1.74 (br s, 3H), 2.20 (m, 1H), 2.98 (m, 2H), 3.36 (t, 2H,  $J$  = 6 Hz), 3.71 (dd, 1H,  $J$  = 3 and 10 Hz), 4.39 (s, 2H), 5.40 (m, 1H), 6.49 (d, 1H,  $J$  = 10.5 Hz), 6.80 (d, 1H,  $J$  = 10.5), 7.26 (s, 5H), 9.50 (s, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 19.527, 23.915, 31.012, 42.444, 42.715, 66.875, 67.796, 68.175, 72.726, 118.665, 123.433, 127.550, 128.200, 133.672, 137.897, 139.089, 141.473, 198.248, 198.356. IR (film)  $\text{cm}^{-1}$ , 3040, 2960, 2915, 2860, 1730, 1690, 1670, 1450, 1365, 1260, 1190, 735, 695.

4a- $\beta$ -Acetyl-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (83)

A 5 mmole scale reaction afforded a 100% yield of 83. NMR ( $\text{CDCl}_3$ ) 1.50 (m, 2H), 1.76 (br s, 3H), 2.37 (s, 3H), 2.96 (m, 2H), 3.35 (t, 2H,  $J$  = 7 Hz), 4.0 (dd, 1H,  $J$  = 3 and 10 Hz), 4.40 (s, 2H), 5.35 (m,



1H), 6.52 (d, 1H,  $J = 10.5$  Hz), 6.82 (d, 1H,  $J = 10.5$  Hz), 7.28 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 19.852, 23.373, 26.786, 26.949, 31.934, 42.715, 44.069, 68.067, 72.617, 122.349, 127.496, 128.146, 134.539, 137.952, 139.252, 139.414, 140.985, 197.544, 198.898, 203.557. IR (film) cm<sup>-1</sup>, 3060, 3040, 2940, 2910, 2880, 1710, 1680, 1610, 1500, 1460, 1440, 1365, 1265, 1190, 1125, 1100, 1030, 910, 860, 745, 700.

4a- $\beta$ -Acetyl-7-methyl-5 $\alpha$ -(acetox)-4a, 5, 8, 8a- $\beta$ -tetrahydronaphthalene-1,4-dione (84)

Compound 84 was isolated in 100% yield on a 5 mmole scale. NMR (CDCl<sub>3</sub>) 1.74 (br s, 3H), 1.82 (s, 3H), 2.42 (s, 3H), 2.88 (m, 1H), 3.06 (m, 1H), 3.95 (d, 1H,  $J = 8$  Hz), 5.76 (br s, 2H), 6.62 (d, 1H,  $J = 10$  Hz), 6.93 (d, 1H,  $J = 10$  Hz). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 20.339, 22.994, 24.565, 27.978, 44.232, 69.150, 117.040, 138.548, 141.473, 141.690, 168.614, 196.135, 196.298, 200.794. IR (film) cm<sup>-1</sup>, 3060, 2980, 2920, 1740-1670, 1610, 1420, 1370, 1220, 1160, 1090, 1015, 960, 730.

General Procedure for Zinc and Acetic Acid Reduction

To a 0.5 M acetic acid solution of the appropriate enedione was added six molar equivalents of zinc dust. The zinc was added portion-wise and the reaction was kept at room temperature by means of a cool water bath. The reaction was stirred for 30 minutes at room temperature following the last addition of zinc. The reaction was filtered and the zinc washed with Et<sub>2</sub>O and quickly washed with chloroform. The reaction was diluted with 3 volumes of chloroform and washed with NaHCO<sub>3</sub> solution

to remove all the acetic acid. The organic solution was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo.

4a- $\beta$ -Carbomethoxy-5 $\alpha$ -(acetic acid t-butyl ester)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (85)

On a 10 mmole scale, compound 85 was prepared in quantitative yield. NMR ( $\text{CDCl}_3$ ) 1.45 (s, 9H), 2.25 (m, 1H), 2.60 (m, 4H), 3.50 (m, 1H), 3.80 (s, 3H), 5.56 (br s, 2H). IR (film)  $\text{cm}^{-1}$ , 3040, 3010, 2995, 2960, 2940, 1730, 1600, 1440, 1395, 1370, 1250, 1155, 990, 840.

4a- $\beta$ -Carbomethoxy-6,8 $\alpha$ -dimethyl-5 $\alpha$ -trimethylsilyloxy-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (86)

Compound 86 was prepared in 98 % yield on a 4.8 mmole scale. NMR ( $\text{CDCl}_3$ ) 0.20 (s, 9H), 1.42 (d, 3H,  $\underline{J}$  = 8 Hz), 1.78 (m, 3H), 2.66 (m, 4H), 3.24 (m, 1H), 3.52 (d, 1H,  $\underline{J}$  = 5 Hz), 3.72 (s, 3H), 4.66 (s, 1H), 5.41 (br s, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 0.515, 17.793, 21.260, 29.982, 35.509, 37.622, 49.485, 52.790, 65.575, 71.534, 128.579, 131.613, 168.994, 204.911, 205.778. IR (film)  $\text{cm}^{-1}$ , 2960, 2880, 1740, 1715, 1430, 1350, 1250, 1180, 1100, 1050, 880, 830, 740. High resolution mass spectrum for  $\text{C}_{17}\text{H}_{26}\text{O}_5\text{Si}$  requires 338.15496, measured 338.1539.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (87)

Compound 87 was produced in 96% yield on a 46 mmole scale. NMR ( $\text{CDCl}_3$ ) 1.44 (m, 2H), 1.73 (br s, 3H), 2.15 (m, 1H), 2.74 (m, 4H), 3.10 (m, 2H), 3.41 (t, 2H,  $\underline{J}$  = 8 Hz), 3.70 (s, 3H), 3.88 (dd, 1H,  $\underline{J}$  = 3 and 10 Hz), 4.44 (s, 2H), 5.28 (m, 1H), 7.32 (s, 5H). 90 MHz

C-13 NMR ( $\text{CDCl}_3$ ) 20.285, 23.481, 31.337, 34.534, 36.376, 40.060, 46.776, 53.115, 64.329, 68.880, 72.563, 118.936, 127.333, 127.550, 128.092, 136.218, 138.060, 169.535, 204.478, 207.349. IR (film)  $\text{cm}^{-1}$ , 3060, 3030, 2950, 2920, 2860, 1740, 1710, 1490, 1440, 1425, 1355, 1215, 1095, 1020, 730, 690. High resolution mass spectrum for  $\text{C}_{22}\text{H}_{26}\text{O}_5$  requires 370.178031, measured 370.178087. Recrystallized from benzene/hexane, mp 75-6 °C. Anal. calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_5$ : C, 71.33; H, 7.08; Found: C, 71.58; H, 7.12.

4a- $\beta$ -Carbomethoxy-7-methyl-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (88)

On a 5 mmole scale, compound 88 was obtained in quantitative yield. NMR ( $\text{CDCl}_3$ ) 1.68 (br s, 3H), 2.40 (m, 4H), 2.82 (m, 4H), 3.54 (t, 1H,  $J = 6$  Hz), 3.77 (s, 3H), 5.32 (m, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 22.940, 27.003, 27.761, 31.934, 35.022, 35.618, 47.155, 47.860, 52.844, 57.937, 117.149, 117.799, 131.342, 170.348, 204.099, 206.266. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3040, 3020, 2970, 2900, 1750, 1725, 1440, 1260-1200, 1060, 980. High resolution mass spectrum for  $\text{C}_{13}\text{H}_{16}\text{O}_4$  requires 236.10486, measured 236.10488. Recrystallized from benzene/hexane, mp 88-95 °C. Anal calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_4$ : C, 66.08; H, 6.83; Found: C, 66.13; H, 6.87.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-ethyl t-butyl dimethylsilyl ether)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (89)

Compound 89 was prepared in 95% yield on a 23 mmole scale. NMR ( $\text{CDCl}_3$ ) 0.00 (s, 6H), 0.88 (s, 9H), 1.30 (m, 2H), 1.73 (br s, 3H),

2.75 (m, 4H), 3.10 (m, 2H), 3.53 (t, 2H,  $J = 7.5$  Hz), 3.71 (s, 3H), 3.88 (m, 1H), 5.24 (m, 1H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 0.00, 18.226, 20.448, 23.644, 25.865, 33.938, 34.805, 35.943, 36.647, 39.627, 47.101, 53.169, 53.277, 61.945, 64.491, 118.774, 136.597, 169.752, 204.532, 207.403. IR (film) cm<sup>-1</sup>, 2960, 2930, 2860, 1750, 1715, 1430, 1250, 1220, 1090, 830, 770.

4a-β-Carbomethoxy-6-methyl-5α-(2-hydroxyethyl)-2, 3, 4a, 5, 8, 8a-β-hexahydronaphthalene-1,4-dione (90)

Compound 90 was obtained in 92% yield on a 10 mmole scale. This compound exists as the hemi-ketal of the C-4 ketone and the 5 -hydroxyethyl side chain. NMR (CDCl<sub>3</sub>) 1.50 (m, 4H), 1.74 (br s, 3H), 2.05 (m, 1H), 2.52 (m, 2H), 2.82 (m, 2H), 3.62 (m, 2H), 3.72 (s, 3H), 5.35 (m, 1H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 21.531, 23.102, 27.436, 36.160, 36.647, 36.755, 41.577, 51.814, 56.203, 59.616, 93.908, 118.557, 136.976, 172.948, 208.974. IR (film) cm<sup>-1</sup>, 3600-3300, 3040, 2960, 2920, 1730, 1710, 1620, 1440, 1250, 1050, 920, 840, 800.

4a-β-Carbomethoxy-6-methyl-5α-(acetic acid ethyl ester)-2, 3, 4a, 5, 8, 8a-β-hexahydronaphthalene-1,4-dione (91)

On a 30 mmole scale, compound 91 was isolated in 96% yield. NMR (CDCl<sub>3</sub>) 1.25 (t, 3H,  $J = 7.5$  Hz), 1.70 (br s, 3H), 2.08 (dd, 2H,  $J = 4$  and 7 Hz), 2.29 (m, 1H), 2.80 (m, 6H), 3.75 (s, 3H), 4.10 (q, 2H,  $J = 7.5$  Hz), 5.30 (m, 1H). IR (film) cm<sup>-1</sup>, 3040, 2960, 2920, 1750, 1730, 1440, 1370, 1350, 1250, 1050, 1020, 930, 860.

4a- $\beta$ -Formyl-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (92)

Compound 92 was prepared in 91% yield on a 4.85 mmole scale. NMR ( $\text{CDCl}_3$ ) 1.2-1.6 (envelope, 2H), 1.76 (br s, 3H), 2.12 (m, 1H), 2.70 (m, 4H), 3.16 (m, 2H), 3.44 (t, 2H,  $J = 7.5$  Hz), 3.83 (dd, 1H,  $J = 3$  and 10 Hz), 5.46 (s, 2H), 5.42 (m, 1H), 7.34 (s, 5H), 9.24 (s, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 19.202, 24.294, 31.391, 34.318, 37.297, 40.494, 43.961, 68.338, 69.529, 72.780, 123.650, 127.604, 127.767, 128.309, 133.943, 138.060, 196.406, 205.128, 208.053. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3060, 3020, 3000, 2980, 1710, 1695, 1410, 1200, 1090. Recrystallized from benzene/hexane, mp 94  $^{\circ}\text{C}$ . Anal. calcd for  $\text{C}_{21}\text{H}_{24}\text{O}_4$ : C, 74.09; H, 7.11; Found: C, 74.30; H, 7.19.

4a- $\beta$ -Acetyl-6-methyl-5 $\alpha$ -(2-ethyl benzyl ether)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydronaphthalene-1,4-dione (93)

Compound 93 was isolated in 93% yield on a 5 mmole scale. NMR ( $\text{CDCl}_3$ ) 1.40 (m, 2H), 1.76 (br s, 3H), 2.26 (s, 3H), 2.38-3.20 (envelope, 7H), 3.42 (t, 2H,  $J = 7.5$  Hz), 4.14 (dd, 1H,  $J = 3$  and 10 Hz), 4.46 (s, 2H), 5.36 (m, 1H), 7.34 (s, 5H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 19.635, 24.077, 24.727, 32.692, 34.589, 36.593, 40.981, 45.315, 68.392, 72.401, 72.726, 122.999, 127.604, 127.767, 128.363, 134.322, 138.345, 202.094, 205.507, 208.920. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3060, 3020, 3000, 2960, 2920, 2860, 1750, 1740, 1420, 1350, 1200, 1090, 970. Recrystallized from benzene/hexane, mp 117  $^{\circ}\text{C}$ . Anal. calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_4$ : C, 74.55; H, 7.39; Found: C, 74.76; H, 7.34.

4a- $\beta$ -Acetyl-7-methyl-5 $\alpha$ -(acetox)-2, 3, 4a, 5, 8, 8a- $\beta$ -hexahydro-naphthalene-1,4-dione (94)

On a 5 mmole scale, compound 94 was isolated in 95% yield. NMR ( $\text{CDCl}_3$ ) 1.76 (s, 3H), 1.92 (s, 3H), 2.38 (s, 3H), 2.72 (m, 4H), 3.02 (m, 2H), 4.02 (d, 1H,  $J = 8$  Hz), 5.74 (m, 1H), 5.78 (d, 1H,  $J = 6$  Hz). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 20.502, 23.156, 24.727, 26.623, 33.938, 34.534, 36.972, 44.394, 69.746, 116.336, 142.502, 168.614, 199.656, 203.936, 205.941. IR (film)  $\text{cm}^{-1}$ , 3020, 2980, 2920, 1750-1700, 1425, 1370, 1310, 1230, 1160, 1110, 1090, 1015, 800.

4a- $\beta$ -Carbomethoxy-5 $\alpha$ -(acetic acid *t*-butyl ester)-2, 3, 4a, 5, 8, 8a- $\alpha$ -hexahydronaphthalene-1,4-dione (95)

Chromatography of the *cis*-diketone 85 on basic alumina (10/1:w/w) using benzene as solvent afforded a 70% yield of 95 on a 10 mmole scale. NMR ( $\text{CDCl}_3$ ) 1.46 (s, 9H), 2.26 (m, 5H), 2.80 (m, 4H), 3.12 (dd, 1H,  $J = 6$  and 10 Hz), 3.62 (s, 3H), 5.78 (m, 2H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 23.915, 28.032, 34.589, 36.810, 38.164, 38.272, 44.394, 52.952, 62.812, 81.123, 125.546, 128.309, 168.560, 170.185, 205.236, 206.103. IR (film)  $\text{cm}^{-1}$ , 3020, 3000, 2970, 1745, 1710, 1400, 1360, 1290, 1250-1200, 1140. Recrystallized from benzene/hexane, mp 102-3  $^{\circ}\text{C}$ .

4a- $\beta$ -Carbomethoxy-6,8 $\alpha$ -dimethyl-5 $\alpha$ -trimethylsilyloxy-2, 3, 4a, 5, 8, 8a- $\alpha$ -hexahydronaphthalene-1,4-dione (96)

Chromatography as above furnished compound 96 in 90% yield on a 4.7 mmole scale. NMR ( $\text{CDCl}_3$ ) 0.20 (s, 9H), 1.22 (d, 3H,  $J = 7$  Hz), 1.82 (m, 3H), 2.56 (m, 1H), 2.74 (m, 4H), 3.26 (d, 1H,  $J = 10$  Hz), 3.60

(s, 3H), 4.72 (s, 1H), 5.26 (m, 1H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 0.515, 20.773, 21.423, 29.657, 34.697, 38.110, 49.918, 52.519, 65.412, 72.563, 130.205, 132.805, 167.856, 205.074, 207.024. IR (film) cm<sup>-1</sup>, 3040, 2975, 2885, 1750, 1725, 1440, 1300, 1250, 1210, 1115, 1060, 910, 870, 840, 750. High resolution mass spectrum for C<sub>17</sub>H<sub>26</sub>O<sub>5</sub>Si requires 338.15496, measured 338.15459.

4a-β-Carbomethoxy-6-methyl-5α-(2-ethyl benzyl ether)-2, 3, 4a, 5, 8, 8a-α-hexahydronaphthalene-1,4-dione (97)

Chromatography of 44 mmol of 87 on basic alumina provided 97 in 79% yield. NMR (CDCl<sub>3</sub>) 1.72 (br s, 3H), 1.76 (m, 2H), 2.32 (m, 3H), 2.62 (m, 4H), 3.30 (dd, 1H,  $J = 3$  and 10 Hz), 3.50 (t, 2H,  $J = 7.5$  Hz), 3.59 (s, 3H), 4.42 (s, 2H), 5.35 (m, 1H), 7.30 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.669, 23.698, 31.282, 34.534, 38.110, 41.956, 43.636, 52.573, 64.112, 68.446, 73.051, 120.237, 127.658, 127.767, 128.309, 136.056, 137.897, 168.939, 205.345, 206.916. IR (film) cm<sup>-1</sup>, 3060, 3020, 3000, 2945, 2920, 2855, 1740, 1710, 1490, 1450, 1355, 1290, 1240, 1215, 1170, 1090, 1020, 925, 800, 735, 690. High resolution mass spectrum for C<sub>22</sub>H<sub>26</sub>O<sub>5</sub> requires 370.17803, measured 370.17636.

4a-β-Carbomethoxy-7-methyl-2, 3, 4a, 5, 8, 8a-α-hexahydronaphthalene-1,4-dione (98)

Chromatography on basic alumina using benzene as the solvent afforded compound 98 in 95% yield. NMR (CDCl<sub>3</sub>) 1.70 (br s, 3H), 2.34 (m, 4H), 2.84 (m, 4H), 3.52 (t, 1H,  $J = 6$  Hz), 3.68 and 3.76 (two s, 3H), 5.36 (m, 1H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.885, 22.994, 23.536,

27.057, 27.815, 28.140, 30.957, 31.988, 35.076, 35.401, 35.509, 35.672, 36.376, 47.210, 47.914, 48.510, 48.943, 52.790, 52.890, 57.991, 59.345, 117.203, 117.907, 131.397, 132.588, 169.156, 170.402, 204.153, 205.724, 206.266. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3040, 3020, 2960, 2920, 2860, 1740, 1725, 1435, 1380, 1300, 1250, 1110, 1070, 1005, 920, 850.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(2-ethyl *t*-butyldimethylsilyl ether)-2, 3, 4a, 5, 8, 8a- $\alpha$ -hexahydronaphthalene-1,4-dione (99)

A 0.25 M benzene solution of 22 mmoles of 89 was treated with 1.1 mmoles of DBN. The reaction was stirred at room temperature for 3 hours. The reaction was washed with 1 N HCl, saturated  $\text{NaHCO}_3$ , and brine. The benzene was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to yield 99 in 88% yield. NMR ( $\text{CDCl}_3$ ) 0.00 (s, 6H), 0.92 (s, 9H), 1.54 (m, 2H), 1.76 (m, 3H), 2.36 (m, 1H), 2.80 (m, 4H), 3.18 (m, 3H), 3.60 (s, 3H), 3.66 (t, 2H,  $J = 7.5$  Hz), 5.32 (m, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 18.226, 22.831, 23.752, 25.648, 25.865, 34.589, 35.130, 38.435, 41.306, 43.852, 52.735, 61.891, 64.112, 119.478, 136.706, 168.831, 205.399, 206.916. IR (film)  $\text{cm}^{-1}$ , 3040, 2960, 2935, 1750, 1715, 1425, 1250, 1220, 1095, 830, 780. High resolution mass spectrum for  $\text{C}_{21}\text{H}_{34}\text{O}_5\text{Si}$  requires 394.21756, measured 394.21769.

4a- $\beta$ -Carbomethoxy-6-methyl-5 $\alpha$ -(acetic acid ethyl ester)-2, 3, 4a, 5, 8, 8a- $\alpha$ -hexahydronaphthalene-1,4-dione (100)

On a 29 mmole scale, compound 91 was epimerized on basic alumina using benzene as solvent in 65% yield. NMR ( $\text{CDCl}_3$ ) 1.28 (t, 3H,  $J = 8$  Hz), 1.77 (br s, 3H), 2.28 (m, 1H), 2.36 (d, 2H,  $J = 6$  Hz), 2.82 (m,



4H), 3.18 (m, 2H), 3.54 (d, 1H,  $J = 6$  Hz), 3.64 (s, 3H), 4.13 (q, 2H,  $J = 8$  Hz), 5.36 (m, 1H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) 13.841, 21.856, 23.536, 34.480, 36.105, 37.947, 40.819, 43.256, 52.627, 60.537, 63.570, 120.345, 135.243, 168.344, 171.486, 204.695, 206.157. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3040, 2960, 2920, 1750, 1725, 1440, 1370, 1350, 1300, 1255, 1230, 1185, 1080, 1025, 805. Recrystallized from benzene/hexane, mp 102 °C. High resolution mass spectrum for  $\text{C}_{17}\text{H}_{22}\text{O}_6$  requires 322.14165, measured 322.13935.

Preparation of (1 $\alpha$ , 2 $\alpha$ )-5-Methyl-6 $\alpha$ -(2-ethyl benzyl ether)-8 -  
hydroxy-11-oxa-12-oxotricyclo[5.3.1.0]dodec-4-ene (102)

A 1.0 M THF solution of 24.66 g (66.65 mmol) of diketone 97 was added dropwise over 35 minutes to a stirred 1.0 M solution of L-selectride containing 200 mmol of hydride. The reaction was allowed to slowly warm to -20 °C and maintained at -20 °C for 12 hours. The excess hydride was quenched with water. The reaction was warmed to ca. 0 °C and 66 mL of 3 M NaOH was added. This was followed by careful addition of 66 mL of 30%  $\text{H}_2\text{O}_2$ . The rate of addition was such that the temperature of the reaction stayed between 15-20 °C. Cooling was maintained by means of an ice bath. After addition of the  $\text{H}_2\text{O}_2$ , the reaction was stirred at room temperature for 8 hours. The reaction was poured into 100 mL of  $\text{H}_2\text{O}$  and extracted well with ether. The combined ether extractions were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using 20% ethyl acetate/hexane as solvent to yield 17.10 g (50 mmol) of 102. Recrystallized from hexane/ethyl acetate,

mp 105-6 °C. NMR (CDCl<sub>3</sub>) 1.52 (m, 2H), 1.74 (br s, 3H), 2.0 (m, 6H), 2.73 (dd, 1H,  $J = 4$  and 8 Hz), 3.56 (t, 2H,  $J = 5.5$  Hz), 3.88 (m, 1H), 4.28 (d, 1H,  $J = 5$  Hz), 4.52 (s, 2H), 5.26 (m, 1H), 7.33 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 23.590, 27.328, 27.815, 29.603, 34.534, 40.060, 55.553, 68.771, 69.042, 69.205, 73.051, 82.856, 119.261, 127.388, 127.658, 128.254, 137.681, 138.168, 177.336. IR (film) cm<sup>-1</sup>, 3450, 3040, 2960, 2880, 1770, 1500, 1460, 1370, 1210, 1100, 1085, 1030, 960, 940, 810, 750, 700. High resolution mass spectrum for C<sub>21</sub>H<sub>26</sub>O<sub>4</sub> requires 342.18312, measured 342.18268.

Preparation of (1 $\alpha$ , 2 $\alpha$ )-5-Methyl-6 $\alpha$ -(2-ethyl benzyl ether)-8 $\alpha$ -(2-tetrahydropyranyloxy)-11-oxa-12-oxotricyclo[5.3.1.0]dodec-4-ene (103)

To a 0.2 M CH<sub>2</sub>Cl<sub>2</sub> solution containing 1.26 g (3.68 mmoles) of alcohol 102 and 0.62 g (7.36 mmoles) of dihydropyran was added 0.185 g (0.74 mmoles) of pyridinium *p*-toluenesulfonate. The reaction was stirred at room temperature for 10 hours. The reaction was poured into an equal volume of ether and washed twice with half-saturated NaCl solution. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to yield 1.55 g (3.68 mmoles) of 103. NMR (CDCl<sub>3</sub>) 1.58 (m, 8H), 1.78 (br s, 3H), 2.0-2.60 (envelope, 7H), 2.88 (m, 1H), 3.52 (dd, 2H,  $J = 7$  and 14 Hz), 3.76-4.12 (envelope, 3H), 4.30 (m, 1H), 5.48 (s, 2H), 4.74 (m, 1H), 5.35 (m, 1H), 7.32 (s, 5H). IR (film) cm<sup>-1</sup>, 3060, 3020, 2940, 2850, 1770, 1485, 1440, 1350, 1200, 1130, 1070, 1020, 970, 890, 860, 800, 720, 690. High resolution mass spectrum for C<sub>26</sub>H<sub>34</sub>O<sub>5</sub> requires 426.24063, measured 426.24064.

Preparation of trans-1, 2, 3, 4, 4a, 5, 8, 8a-Octahydro-4a-(hydroxymethyl)-4 $\alpha$ -(2-tetrahydropyranyloxy)-5 $\alpha$ -(2-ethyl Benzyl Ether)-6-methylnaphthalene-1 $\beta$ -ol (104)

A 1.0 M ether solution of 2.66 g (6.26 mmol) of lactone 103 was added dropwise over 3 minutes to a stirred suspension of 0.36 g (9.48 mmol) of lithium aluminum hydride and 30 mL of ether. The reaction was stirred 8 hours at room temperature. Hydrolysis was performed by careful addition of 0.36 mL of H<sub>2</sub>O, followed by 0.36 mL of 15% NaOH and 1.08 mL of H<sub>2</sub>O. The reaction was stirred until the precipitate became granular. The precipitate was filtered and washed with ether. The filtrate was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to yield 2.66 g (6.20 mmol) of 104. NMR (CDCl<sub>3</sub>) 1.52 (envelope, 8H), 1.70 (br s, 3H), 1.80-2.50 (envelope, 8H), 3.60 (m, 5H), 3.92 (m, 3H), 4.48 (s, 2H), 4.56 (m, 1H), 5.34 (m, 1H), 7.30 (s, 5H). IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3380, 3030, 3000, 2940, 2860, 1490, 1450, 1350, 1210, 1170, 1110, 1070, 1020, 970, 905, 865, 690. High resolution mass spectrum for C<sub>26</sub>H<sub>38</sub>O<sub>5</sub> requires 430.27193, measured 430.27202.

Preparation of trans-1, 2, 3, 4, 4a, 5, 8, 8a-Octahydro-4a-(hydroxymethyl)-5 $\alpha$ -(2-ethyl Benzyl Ether)-6-methylnaphthalene-1 $\beta$ ,4 $\alpha$ -diol (105)

To a solution of 2.37 g (5.5 mmol) of THP-ether 104 and 45 mL of CH<sub>3</sub>OH was added 0.276 g (1.10 mmol) of pyridinium p-toluenesulfonate. The reaction was stirred at 50 °C for 6 hours. It was concentrated in vacuo and the residue chromatographed on silica gel (5/1; w/w) using ethyl acetate/hexane as the solvent to afford 1.90 g (5.5 mmol) of 105.

NMR (CDCl<sub>3</sub>) 1.40-2.40 (envelope, 13H), 1.66 (br s), 3.64 (m, 4H), 4.0-4.20 (m, 2H), 4.54 (s, 2H), 5.28 (m, 1H), 7.32 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.940, 25.865, 26.028, 30.795, 32.259, 37.460, 40.006, 44.611, 62.053, 67.742, 71.100, 72.509, 73.159, 119.370, 127.713, 128.309, 136.597, 137.681. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3600, 3400, 3020, 3000, 2960, 2800, 1505, 1465, 1440, 1350, 1220, 1190, 1090, 1070, 1030, 920.

Preparation of (4α)-2α-Phenylselenenyl-10α-(2-ethyl Benzyl Ether)-1α-methyl-11-oxatricyclo[7.2.1.0]dodecane-5β,8α-diol (106)

A 1.0 M CH<sub>2</sub>Cl<sub>2</sub> of 1.16 g (6.05 mmoles) of phenylselenenyl chloride was added dropwise over 3 minutes to a stirred solution of 1.90 g (5.5 mmoles) of 105 and 50 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. The reaction was allowed to slowly warm to room temperature. Thin layer chromatography was used to judge when the reaction was complete. The CH<sub>2</sub>Cl<sub>2</sub> was removed and the residue chromatographed on silica gel (10/1; w/w) using ethyl acetate/hexane as the solvent. The reaction yielded 2.28 g (4.56 mmoles) of 106. NMR (CDCl<sub>3</sub>) 1.54 (s, 3H), 1.62-2.10 (m, 10H), 2.78 (m, 1H), 3.08 (m, 1H), 3.38-3.80 (envelope, 5H), 3.88 (d, 1H, J = 8 Hz), 4.42 (d, 1H, J = 8 Hz), 4.56 (s, 2H), 7.26 (m, 3H), 7.34 (s, 5H), 7.48 (m, 2H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 23.752, 25.215, 25.973, 31.771, 32.747, 34.697, 47.047, 50.514, 67.796, 69.259, 69.475, 70.559, 73.538, 83.344, 127.225, 128.038, 128.634, 129.230, 132.968. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3620, 3450, 3060, 3000, 2970, 2940, 2880, 1570, 1470, 1450, 1435, 1375, 1360, 1200, 1070, 1000, 920.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-11-oxatricyclo  
[7.2.1.0]dodec-2-ene-5 $\beta$ ,8 $\alpha$ -diol (107)

To a 0.10 M CH<sub>2</sub>Cl<sub>2</sub> solution of 0.40 g (0.80 mmoles) of 106 was added 0.23 g (2 mmoles) of 30% H<sub>2</sub>O<sub>2</sub> in two portions. The reaction was stirred vigorously at room temperature for 20 minutes. The completion of the reaction was judged by thin layer chromatography. When complete, the reaction was poured into CH<sub>2</sub>Cl<sub>2</sub> and washed with 10% K<sub>2</sub>CO<sub>3</sub>. The CH<sub>2</sub>Cl<sub>2</sub> was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using ethyl acetate/hexane as the eluent. The reaction yielded 0.22 g (0.63 mmoles) of 107. NMR (CDCl<sub>3</sub>) 1.28 (s, 3H), 1.62 (m, 5H), 1.90-2.22 (envelope, 3H), 2.76 (m, 1H), 3.60 (m, 4H), 3.96 (dd, 1H, J = 2 and 8 Hz), 4.10 (br s, 1H), 4.54 (s, 2H), 4.68 (d, 1H, J = 8 Hz), 5.65 (s, 2H), 7.34 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.615, 23.861, 26.515, 31.282, 44.286, 44.557, 51.056, 66.767, 68.230, 69.205, 69.529, 72.997, 79.606, 127.658, 127.984, 128.254, 129.934, 132.426, 137.572. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3595, 3410, 3060, 3020, 2990, 2930, 2860, 1485, 1440, 1430, 1370, 1350, 1200, 1080, 1060, 1010, 980, 945, 850, 810. High resolution mass spectrum for C<sub>21</sub>H<sub>28</sub>O<sub>4</sub> requires 344.19877, measured 344.19890.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-11-oxatricyclo  
[7.2.1.0]dodec-2-ene-5 $\beta$ ,8 $\alpha$ -di- $\beta$ -methoxyethoxymethyl ether (108a)

A 0.20 M CH<sub>2</sub>Cl<sub>2</sub> solution containing 0.12 g (0.35 mmoles) of 107 was treated with 0.135 g (1.05 mmoles) of N,N-diisopropyl ethyl amine and 0.13 g (1.05 mmoles) of methoxyethoxymethyl chloride. The reaction

was stirred at room temperature for 12 hours. The  $\text{CH}_2\text{Cl}_2$  solution was poured into 30 mL of ether and washed successively with  $\text{H}_2\text{O}$ , 1 N HCl, saturated  $\text{NaHCO}_3$ , and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using hexane/ethyl acetate as solvent to yield 0.18 g (0.35 mmoles). NMR ( $\text{CDCl}_3$ ) 1.28 (s, 3H), 1.40-2.30 (envelope, 8H), 3.43 (s, 6H), 3.75 (m, 13H), 4.56 (s, 2H), 4.78 (s, 2H), 4.88 (s, 2H), 5.70 (m, 2H), 7.43 (s, 5H). IR (film)  $\text{cm}^{-1}$ , 3020, 2920, 2880, 2820, 1440, 1355, 1190, 1160, 1090, 1030, 975, 935, 840, 725, 690.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-11-oxatricyclo  
[7.2.1.0]-5 $\beta$ ,8 $\alpha$ -diacetoxydodec-2-ene (108b)

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution containing 0.05 g (0.145 mmoles) of diol 107 was added 0.040 g (0.4 mmoles) of triethylamine, 0.0043 g (0.035 mmoles) of 4-dimethylaminopyridine, and 0.035 g (0.348 mmoles) of acetic anhydride. The reaction was stirred at room temperature for 10 hours. It was then poured into 25 mL of ether and washed with  $\text{H}_2\text{O}$ , 1 N HCl, saturated  $\text{NaHCO}_3$ , and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo to yield 0.584 g (0.136 mmoles) of 108b. NMR ( $\text{CDCl}_3$ ) 1.30 (s, 3H), 1.50-1.90 (m, 5H), 1.98 (s, 3H), 2.06 (s, 3H), 2.52 (m, 1H), 3.52 (m, 2H), 4.03 (dd, 1H,  $\underline{J}$  = 2 and 8 Hz; irradiation at 2.52, d, 1H,  $\underline{J}$  = 8 Hz), 4.48 (s, 2H), 4.50 (d, 1H,  $\underline{J}$  = 8 Hz), 4.90 (dd, 1H,  $\underline{J}$  = 4 and 10 Hz), 5.27 (m, 1H), 5.58 (s, 2H), 7.32 (s, 5H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3060, 3020, 3000, 2960, 2860, 1730, 1480, 1470, 1440, 1430, 1360, 1350, 1240-1190, 1110, 1080, 1020, 970, 940, 855, 680.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-11-oxatricyclo[7.2.1.0]dodecane-5 $\beta$ ,8 $\alpha$ -diol (109)

A 0.20 M CH<sub>2</sub>Cl<sub>2</sub> solution of 3.44 g (10 mmoles) of diol 107 was treated with 2.23 g (11 mmoles) of 85% m-chloroperoxybenzoic acid. The reaction was stirred at room temperature for 40 hours. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed successively with saturated NaHCO<sub>3</sub>, 10% NaHSO<sub>3</sub>, saturated NaHCO<sub>3</sub>, and brine. The CH<sub>2</sub>Cl<sub>2</sub> solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield 3.59 g (10 mmoles) of epoxide 109. NMR (CDCl<sub>3</sub>) 1.43 (s, 3H), 1.50-2.00 (envelope, 8H), 2.88 (d, 1H, J = 4 Hz), 3.22 (dd, 1H, J = 3 and 4 Hz; irradiation at 2.88, d, 1H, J = 3 Hz), 3.54 (m, 4H), 3.78 (d, 1H, J = 8 Hz), 4.50 (s, 2H), 4.54 (d, 1H, J = 8 Hz), 7.32 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.777, 23.806, 26.949, 31.228, 33.180, 40.548, 45.315, 49.322, 52.627, 55.445, 67.688, 69.367, 70.504, 71.100, 73.538, 78.793, 128.038, 128.146, 128.634, 137.464. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3580, 3460, 3060, 2995, 2930, 2860, 1485, 1440, 1370, 1350, 1315, 1210, 1145, 1060, 1005, 970, 945, 895, 860, 680. High resolution mass spectrum for C<sub>21</sub>H<sub>28</sub>O<sub>5</sub> requires 360.19368, measured 360.19363.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-11-oxatricyclo[7.2.1.0]dodecane-5 $\beta$ ,8 $\alpha$ -di- $\beta$ -methoxyethoxymethyl ether (110)

To a 0.20 M CH<sub>2</sub>Cl<sub>2</sub> solution containing 1.19 g (3.32 mmoles) of 109 was added 1.72 g (13.28 mmoles) of N,N-diisopropylethylamine and 1.66 g (13.28 mmoles) of methoxyethoxymethyl chloride. The reaction was stirred at room temperature for 18 hours. The reaction was poured into

$\text{CH}_2\text{Cl}_2$  and washed with  $\text{H}_2\text{O}$  and brine. The organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was chromatographed on silica gel (10/1; w/w) using ethyl acetate as solvent to yield 1.78 g (3.32 mmol) of 110. NMR ( $\text{CDCl}_3$ ) 1.43 (s, 3H), 1.50-2.0 (envelope, 8H), 2.84 (d, 1H,  $J = 4$  Hz), 3.14 (m, 1H), 3.36 (s, 3H), 3.38 (s, 3H), 3.40-3.90 (envelope, 11H), 4.50 (s, 2H), 4.72 (s, 2H), 4.79 (s, 2H), 7.32 (s, 5H). IR (film)  $\text{cm}^{-1}$ , 3030, 2940, 2880, 2820, 1450, 1360, 1255, 1195, 1170, 1100, 1030, 980, 940, 870, 840, 730, 690. High resolution mass spectrum for  $\text{C}_{29}\text{H}_{44}\text{O}_9$  requires 536.29855, measured 536.30095.

#### Attempted Openings of Epoxide 110

To a 0.10 M  $\text{CH}_3\text{CN}$  solution of 0.109 g (0.203 mmol) of epoxide 110 was added 0.04 g (0.406 mmol) of KOAc and 0.0108 g (0.041 mmol) of 18-crown-6. The reaction was stirred at room temperature for 24 hours. It was then refluxed for 12 hours. The reaction was poured into ether and washed with  $\text{H}_2\text{O}$  and brine. The ether was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Analysis of the NMR revealed the presence of the epoxide hydrogens at  $\delta$  2.84 and 3.14.

A 0.10 M DMSO solution of 0.109 g (0.203 mmol) of epoxide 110 was treated with 0.06 g (0.812 mmol)  $\text{KO}_2$  and 0.04 g (0.16 mmol) 18-crown-6. The reaction was stirred at room temperature for 12 hours. It was then poured into ether and washed with  $\text{H}_2\text{O}$  and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The epoxide was still intact; as judged by analysis of the NMR spectrum.



To a 1.0 M ether suspension of 0.196 g (1.76 mmol) of *t*-butoxide was added 0.0082 g (0.453 mmol) of H<sub>2</sub>O (66). The reaction was stirred for 10 minutes and then a 1.0 M ether solution of 0.109 g (0.203 mmol) of epoxide 110 was added all at once. The reaction was stirred at room temperature for 10 hours. To the solution was added 0.0108 g (0.041 mmol) of 18-crown-6. Stirring was continued at room temperature for an additional 8 hours. The reaction was poured into ether and washed with H<sub>2</sub>O and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Examination of the NMR spectrum revealed no reaction had occurred.

A 0.30 M dimethoxyethane (DME) suspension of 0.109 g (0.976 mmol) of *t*-butoxide was treated with 0.005 g (0.272 mmol) of H<sub>2</sub>O. The reaction was stirred for 5 minutes at room temperature. To the reaction, was added 0.0654 g (0.122 mmol) of 110 in 1 mL of DME. The reaction was refluxed for 18 hours. It was then poured into ether and washed with H<sub>2</sub>O and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. There was no reaction as determined by NMR analysis.

A suspension of 1.58 g of Woelm Neutral Alumina Activity 1 and 4 mL of Et<sub>2</sub>O was treated with 0.063 g (1.05 mmol) of acetic acid (67). The suspension was stirred at room temperature for 5 minutes; then 0.113 g (0.21 mmol) of epoxide 110 in 1 mL of ether was added. The reaction was stirred at room temperature for 36 hours. The suspension was poured into 50 mL of CH<sub>3</sub>OH and allowed to stand for 4 hours. The CH<sub>3</sub>OH solution was filtered through Celite. The Celite was washed with CH<sub>3</sub>OH. The solution was concentrated and the residue dissolved in ether. The ether

was washed with saturated  $\text{NaHCO}_3$  and brine. The organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. NMR analysis revealed no reaction had taken place.

A reaction exactly the same as above, except DME was substituted for ether, was set up. The reaction was refluxed for 18 hours. The work-up was identical to the previous one. No reaction had occurred; evidenced by the presence of epoxide hydrogens in the NMR spectrum.

The impregnated alumina reaction was again set up the same as the previous two reactions using ether as solvent and 0.963 g (1.97 mmol) of  $\text{CH}_3\text{OH}$  as the doping agent. The reaction was stirred for 36 hours. It was then worked up as before. Analysis of the NMR spectrum indicated no reaction had occurred.

A 0.10 M acetone solution of 0.113 g (0.21 mmol) of 110 was treated successively with 0.15 mL of  $\text{H}_2\text{O}$  and 0.15 mL of 70%  $\text{HClO}_4$ . The reaction was stirred at room temperature for 27 hours. It was then poured into ether and washed with saturated  $\text{NaHCO}_3$ . The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to yield an unidentifiable mixture of products.

A 0.10 M acetone solution of 0.113 g (0.21 mmol) of 110 was treated successively with 1.0 mL of  $\text{H}_2\text{O}$  and 0.30 mL of concentrated  $\text{H}_2\text{SO}_4$ . The solution was stirred at room temperature for 20 hours. The reaction was then worked up in the same manner as the previous experiment. The reaction afforded an uncharacterizable mixture of products.

To a 0.10 M acetone solution containing 0.113 g of 110 was added 0.246 g (1.26 mmol) of benzyltrimethylammonium formate. The reaction

was refluxed for 36 hours. Work up of the reaction in a similar manner as the previous two experiments yielded starting material.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Hydroxyethyl)-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-11-oxatricyclo[7.2.1.0]dodecane-5 $\beta$ ,8 $\alpha$ -di- $\beta$ -methoxyethoxymethyl Ether (111)

To 0.32 g of 10% Pd/C in 15 mL of CH<sub>3</sub>OH was added 1.78 g (3.32 mmoles) of 110 in 5 mL of CH<sub>3</sub>OH. The reaction was stirred at room temperature in an atmosphere of H<sub>2</sub> for 1 hour. The CH<sub>3</sub>OH solution was filtered through a pad of Celite. The Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo to yield 1.44 g (3.23 mmoles) of alcohol 111. NMR (CDCl<sub>3</sub>) 1.48 (s, 3H), 1.50-2.14 (m, 8H), 2.85 (d, 1H, J = 4 Hz), 3.14 (m, 1H), 3.38 (s, 3H), 3.40 (s, 3H), 3.50-3.94 (envelope, 11H), 4.74 (envelope, 5H). IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3620, 3450, 3000, 2940, 2894, 2820, 1460, 1445, 1410, 1370, 1360, 1220, 1170, 1100, 1030, 980, 955, 940, 900, 870, 840. High resolution mass spectrum for C<sub>22</sub>H<sub>38</sub>O<sub>9</sub> requires 446.251594, measured 446.251434.

Preparation of (4 $\alpha$ )-10 $\alpha$ -Acetic Acid-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-11-oxatricyclo[7.2.1.0]dodecane-5 $\beta$ ,8 $\alpha$ -di- $\beta$ -methoxyethoxymethyl Ether (112)

To 0.248 g (0.556 mmoles) of 111 in 10 mL of acetone at 0 °C was added 0.28 mL of 4 M Jones' reagent. The reaction was warmed to room temperature and allowed to stir for 15 minutes. A few drops of isopropanol were added to destroy any excess oxidant. The acetone was removed on the rotary evaporator. The salts were dissolved in a minimum of saturated NaCl. The aqueous layer was exhaustively extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to

yield 0.25 g (0.54 mmol) of 112. NMR ( $\text{CDCl}_3$ ) 1.45 (s, 3H), 1.50-2.00 (envelope, 5H), 2.22-2.50 (envelope, 3H), 2.86 (d, 1H,  $J = 4$  Hz), 3.18 (m, 1H), 3.40 (s, 6H), 3.50-3.90 (envelope, 8H), 4.22 (m, 2H), 4.80 (br s, 4H). IR (film)  $\text{cm}^{-1}$ , 3500-3000, 2920, 2860, 1720, 1440, 1405, 1360, 1230, 1160, 1090, 1020, 945, 865, 835.

Preparation of (1 $\beta$ , 3 $\alpha$ , 12 $\beta$ )-11 $\alpha$ -Methyl-10, 13-dioxo-14-oxotetracyclo [7.4.3.1.0]pentadecan-2 $\beta$ -ol-4 $\beta$ ,7 $\alpha$ -di- $\beta$ -methoxyethoxymethyl Ether (113)

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution containing 0.89 g (1.93 mmol) of 112 was added 0.50 mL of trifluoroacetic acid. The reaction was stirred at room temperature for 24 hours. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with  $\text{H}_2\text{O}$ , 10%  $\text{NaHCO}_3$ , and brine. The  $\text{CH}_2\text{Cl}_2$  solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using ethyl acetate/hexane as the solvent to yield 0.45 g (0.98 mmol) of 113. NMR ( $\text{CDCl}_3$ ) 1.50 (s, 3H), 1.54 (m, 2H), 1.86 (m, 2H), 2.38 (m, 4H), 2.66 (m, 2H), 3.38 (s, 6H), 3.66 (m, 9H), 4.12 (m, 3H), 4.60 (m, 2H), 4.80 (br s, 4H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3460, 3000, 2920, 2880, 2820, 1725, 1450, 1410, 1360, 1230-1200, 1160, 1100, 1020, 950, 920, 840.

#### Attempted Protections of Alcohol 113

To 0.2 M DMF solution containing 0.10 g (0.22 mmol) of 113 and 0.037 g (0.55 mmol) of imidazole was added 0.05 g (0.33 mmol) of t-butyldimethylsilyl chloride. The reaction was heated to 50  $^\circ\text{C}$  and stirred for 24 hours. The reaction was poured into 5 mL of  $\text{H}_2\text{O}$  and extracted with ether. The combined ether extractions were

washed with  $\text{H}_2\text{O}$  and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo to yield 0.10 g of unreacted starting material.

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution of 0.0665 g (0.145 mmol) of 113 and 0.024 g (0.29 mmol) of dihydropyran was added 0.007 g (0.029 mmol) of pyridinium p-toluenesulfonate. The reaction was stirred at room temperature for 12 hours. It was then poured into ether and washed with a half-saturated NaCl solution. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford an identifiable mixture of products.

To a 0.40 M THF suspension of 0.012 g (0.496 mmol) of mineral oil free NaH was added 2 mL of HMPA. To this, was added 0.19 g (0.413 mmol) of 113 in 1 mL of THF. The reaction was stirred at room temperature for 30 minutes. After this 0.0777 g (0.454 mmol) of benzyl bromide was added and the reaction stirred at room temperature for 12 hours. The reaction was poured into ether and washed with  $\text{H}_2\text{O}$  and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo to yield 0.15 g of an unidentifiable product.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-5 $\beta$ ,8 $\alpha$ -diacetoxy-11-oxatricyclo[7.2.1.0]dodecane (114)

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution containing 0.567 g (1.58 mmol) of diol 109 was added 0.43 g (4.26 mmol) of triethylamine, 0.096 g (0.79 mmol) of 4-dimethylaminopyridine, and 0.388 g (3.8 mmol) of acetic anhydride. The reaction was stirred at room temperature for 10 hours.

To the reaction was added 1 mL of  $\text{CH}_3\text{OH}$  to destroy the excess acetic anhydride. It was then diluted with ether and washed with  $\text{H}_2\text{O}$ , 1 N  $\text{HCl}$ , saturated  $\text{NaHCO}_3$ , and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using ethyl acetate/hexane as eluent to afford 0.591 g (1.33 mmoles) of 114. NMR ( $\text{CDCl}_3$ ) 1.47 (s, 3H), 1.50-1.90 (envelope, 5H), 1.97 (s, 3H), 2.02 (m, 3H), 2.17 (s, 3H), 2.88 (d, 1H,  $\underline{J}$  = 4 Hz), 3.22 (m, 1H), 3.55 (t, 2H,  $\underline{J}$  = 7.5 Hz), 3.90 (d, 1H,  $\underline{J}$  = 8 Hz), 4.56 (s, 2H), 4.56 (d, 1H,  $\underline{J}$  = 8 Hz), 4.92 (m, 1H), 5.63 (m, 1H), 7.50 (s, 5H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3020, 3000, 2960, 1730, 1475, 1355, 1230-1190, 1080, 980, 940, 850.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-hydroxyethyl)-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-5 $\beta$ ,8 $\alpha$ -diacetoxy-11-oxatricyclo[7.2.1.0]dodecane (115)

To 0.06 g of 10% Pd/C in 6 mL of  $\text{CH}_3\text{OH}$  was added 0.59 g (1.33 mmoles) of 114 in 4 mL of  $\text{CH}_3\text{OH}$ . The reaction was stirred at room temperature in an atmosphere of  $\text{H}_2$  for 1 hour. The  $\text{CH}_3\text{OH}$  solution was filtered through a pad of Celite. The Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo to yield 0.46 g (1.30 mmoles) of alcohol 115. NMR ( $\text{CDCl}_3$ ) 1.50 (s, 3H), 1.60-2.03 (envelope, 8H), 2.10 (s, 3H), 2.20 (s, 3H), 2.90 (d, 1H,  $\underline{J}$  = 4 Hz), 3.28 (m, 1H), 3.68 (t, 2H,  $\underline{J}$  = 7.5 Hz), 3.90 (d, 1H,  $\underline{J}$  = 8 Hz), 4.58 (d, 1H,  $\underline{J}$  = 8 Hz), 4.94 (m, 1H), 5.70 (m, 1H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3615, 3460, 2995, 2890, 1730, 1480, 1230-1200, 1080, 980, 945, 850.

Preparation of (4 $\alpha$ )-10 $\alpha$ -Acetaldehyde-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-5 $\beta$ ,8 $\alpha$ -diacetoxy-  
11-oxatricyclo[7.2.1.0]dodecane (116)

To a 0.35 M CH<sub>2</sub>Cl<sub>2</sub> suspension of 0.1543 g (0.716 mmol) of pyridinium chlorochromate was added 0.0088 g (0.107 mmol) of sodium acetate. To this was added 0.1266 g (0.358 mmol) of 115 in 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at room temperature for 2 hours. The reaction was diluted with ether and filtered through a short column of silica gel. The residue in the flask was washed with more ether. The ether washings were filtered through the silica gel column. The column was flushed with ether until no more product came through. Concentration of the filtered ether solutions afforded 0.1052 g (0.30 mmol) of aldehyde 116. NMR (CDCl<sub>3</sub>) 1.38 (s, 3H), 1.66-2.0 (envelope, 6H), 2.12 (s, 3H), 2.16 (s, 3H), 2.44 (m, 2H), 2.84 (d, 1H,  $J$  = 4 Hz), 3.23 (m, 1H), 3.89 (d, 1H,  $J$  = 8 Hz), 4.54 (d, 1H,  $J$  = 8 Hz), 4.73 (m, 1H), 5.59 (m, 1H), 9.67 (m, 1H). IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3000, 2980, 2920, 1735, 1425, 1385, 1250-1200, 1115, 1030, 990, 960, 880.

Preparation of (4 $\alpha$ )-10 $\alpha$ -Acetic Acid-1 $\alpha$ -methyl-2,3 $\beta$ -oxido-5 $\beta$ ,8 $\alpha$ -diacetoxy-  
11-oxatricyclo[7.2.1.0]dodecane (117)

To a 0.36 M *t*-butanol solution of 0.128 g (0.36 mmol) of 116 was added 0.602 g (8.6 mmol) of isobutylene. To this was added 0.049 g (0.43 mmol) of sodium chlorite in 1 mL of a buffered (pH = 4) NaH<sub>2</sub>PO<sub>4</sub> solution. The reaction was stirred vigorously for 2 hours. The solution was made basic (pH = 10) and the *t*-butanol removed in vacuo. The residue was extracted with ether to remove neutral impurities. The aqueous layer was acidified with 6 N HCl and extracted with CHCl<sub>3</sub>.

The  $\text{CHCl}_3$  solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford 0.109 g (0.30 mmol) of 117. NMR ( $\text{CDCl}_3$ ) 1.48 (s, 3H), 1.70-2.10 (envelope, 6H), 2.12 (s, 3H), 2.20 (s, 3H), 2.35 (m, 2H), 2.90 (d, 1H,  $J = 4$  Hz), 3.30 (m, 1H), 3.94 (d, 1H,  $J = 8$  Hz), 4.60 (d, 1H,  $J = 8$  Hz), 4.80 (m, 1H), 5.68 (m, 1H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3500-3020, 2995, 2860, 1730-1700, 1405, 1370, 1210, 1140, 1095, 1020, 950.

Preparation of (1 $\beta$ , 3 $\alpha$ , 12 $\beta$ )-4 $\beta$ ,7 $\alpha$ -Diacetoxy-11 $\alpha$ -methyl-10,13-dioxo-14-oxotetracyclo[7.4.3.1.0]pentadecan-2 $\beta$ -ol (118)

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution containing 0.5666 g (1.54 mmol) of 117 was added 0.40 mL of trifluoroacetic acid. The reaction was stirred at room temperature for 24 hours. The reaction was poured into  $\text{CH}_2\text{Cl}_2$  and washed with  $\text{H}_2\text{O}$ , 10%  $\text{NaHCO}_3$ , and brine. The  $\text{CH}_2\text{Cl}_2$  solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (10/1; w/w) using ethyl acetate/hexane as the solvent to yield 0.353 g (0.96 mmol) of 118. NMR ( $\text{CDCl}_3$ ) 1.51 (s, 3H), 1.68-1.96 (envelope, 6H), 2.06 (s, 3H), 2.10 (s, 3H), 2.76 (m, 2H), 4.00 (dd, 1H,  $J = 2$  and 8 Hz), 4.12 (m, 1H), 4.70 (d, 1H,  $J = 8$  Hz), 4.76-5.00 (envelope, 2H), 5.56 (m, 1H). IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3520, 3000, 2960, 2875, 1750-1710, 1440, 1410, 1370, 1250-1160, 1100, 1075, 960, 920.

Attempted Protections of 118

To a 0.10 M  $\text{CH}_2\text{Cl}_2$  solution of 0.10 g (0.29 mmol) of 118 was added 0.09 g (0.58 mmol) of chloromethyl benzyl ether and 0.075 g (0.58 mmol) of diisopropylethylamine. The reaction was refluxed for



12 hours. An additional 0.14 g (0.87 mmol) of chloromethyl benzyl ether and 0.11 g (0.87 mmol) of diisopropylethylamine were added. Refluxing was continued for 24 hours. After this period there was no apparent sign of success. The reaction was poured into 25 mL of ether and washed with  $\text{H}_2\text{O}$ , 1 N HCl, saturated  $\text{NaHCO}_3$  and brine. The ether solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield 0.095 g of starting material.

To a 0.38 M  $\text{CH}_3\text{CN}$  solution of 0.14 g (0.38 mmol) of 118 was added 0.033 g (0.42 mmol) of pyridine. To this was added 0.085 g (0.396 mmol) of *t*-butyl dimethylsilyl perchlorate. The reaction was stirred at room temperature for 8 hours. Then an additional 0.033 g (0.42 mmol) of pyridine and 0.085 g (0.396 mmol) of *t*-butyldimethylsilyl perchlorate were added. The reaction was stirred at room temperature for an additional 8 hours. After this period there was no perceptible sign of reaction. The reaction was worked up similar to the previous reaction. Concentration of the ether solution afforded 0.14 g of starting material.

Preparation of 4a- $\beta$ -Carbomethoxy-5-methyl-6,7-oxido-5 $\alpha$ -(2-ethyl Benzyl Ether)-2, 3, 4a, 5, 8, 8a- $\alpha$ -hexahydronaphthalene-1,4-dione (119)

A 0.30 M  $\text{CH}_2\text{Cl}_2$  solution containing 2.44 g (6.6 mmol) of 97 was cooled to 0 °C. With stirring, 1.47 g (7.25 mmol) of 85% *m*-chloroperoxybenzoic acid was added. The reaction was allowed to slowly warm to room temperature and stir overnight. The solution was poured into 75 mL of ether and washed with saturated  $\text{NaHCO}_3$ , 10%  $\text{NaHSO}_3$ , saturated

NaHCO<sub>3</sub>, and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to yield 2.51 g (6.5 mmol) of 119. NMR (CDCl<sub>3</sub>) 1.46 (s, 3H), 1.52-2.00 (envelope, 4H), 2.74 (br s, 4H), 3.02 (m, 3H), 3.64 (s, 3H), 3.68 (m, 2H), 4.52 (s, 2H), 7.32 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 23.802, 24.647, 27.053, 34.987, 38.564, 38.694, 41.424, 52.675, 59.828, 60.153, 61.844, 67.826, 68.022, 72.639, 127.590, 128.175, 137.995, 169.405, 206.017, 206.667. IR (film) cm<sup>-1</sup>, 3040, 2960, 2880, 1750, 1725, 1440, 1380, 1310, 1250, 1200, 1100, 1030, 740, 700.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-5, 8, 12-trioxo-11-oxatricyclo[7.2.1.0]dodecan-2 $\alpha$ -ol (120)

A 0.20 M THF solution containing 5.02 g (13 mmol) of 119 was treated with 4 mL of 3 N HClO<sub>4</sub>. The reaction was stirred at room temperature for 5 hours. The reaction was then poured into 100 mL of ether and washed with saturated NaHCO<sub>3</sub> and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to yield 4.39 g (11.8 mmol) of 120. NMR (CDCl<sub>3</sub>) 1.56 (s, 3H), 1.90-2.22 (envelope, 4H), 2.50 (m, 3H), 2.72 (m, 2H), 3.04 (dd, 1H, J = 4 and 11 Hz), 3.46 (m, 2H), 3.92 (m, 1H), 4.34 (s, 2H), 7.32 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 20.352, 24.841, 29.523, 35.896, 37.782, 39.853, 49.812, 61.907, 69.321, 70.036, 72.573, 86.749, 127.914, 128.369, 137.538, 173.696, 202.309, 207.309. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3620, 3460, 3040, 2980, 2880, 1770, 1720, 1450, 1410, 1380, 1360, 1260, 1100, 1050, 980, 905.

Preparation of (4 $\beta$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2,5 $\alpha$ -epoxy-5 $\beta$ -t-butyldimethylsilyloxy-8, 12-dioxo-11-oxatricyclo[7.2.1.0]dodecane  
(121)

To a 0.50 M DMF solution containing 1.55 g (4.16 mmol) of 120 was added 0.845 g (12.4 mmol) of imidazole and 1.06 g (7.03 mmol) of t-butyldimethylsilyl chloride. The reaction was heated to 40 °C and stirred at this temperature for 24 hours. The reaction was poured into 40 mL of H<sub>2</sub>O and extracted four times with 75-mL portions of ether. The combined ether extractions were washed with H<sub>2</sub>O and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexane to yield 1.62 g (3.33 mmol) of 121, mp 147 °C. NMR (CDCl<sub>3</sub>) 0.14 (s, 3H), 0.18 (s, 3H), 1.00 (s, 9H), 1.56 (s, 3H), 1.92 (m, 2H), 2.28 (m, 2H), 2.40-2.72 (envelope, 3H), 2.90 (m, 3H), 3.24 (m, 1H), 3.44 (m, 1H), 3.88 (m, 1H), 4.32 (s, 2H), 7.30 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 18.076, 20.938, 25.752, 25.882, 28.223, 30.239, 38.758, 49.681, 61.063, 69.711, 70.361, 72.833, 86.554, 105.283, 127.719, 128.304, 137.733, 147.163, 173.891, 204.195. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3020, 2960, 2940, 2900, 2880, 1775, 1725, 1680, 1460, 1415, 1370, 1260-1200, 1100, 1060, 940, 895, 840.

Preparation of (4 $\beta$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2,5 $\alpha$ -epoxy-5 $\beta$ -t-butyldimethylsilyloxy-11-oxatricyclo[7.2.1.0]dodecan-8 $\alpha$ ,12-diol (122)

A 0.20 M THF solution containing 4.0 g (8.23 mmol) of 121 was cooled to -78 °C. To this was added 33 mL of 1.0 M hexane solution of diisobutylaluminum hydride (33 mmol) over a period of 15 minutes. The reaction was stirred at -78 °C for 2 hours. It was then allowed to

slowly warm to room temperature and stir at room temperature for 2 hours. The reaction was then poured into a vigorously stirred two phase system of 50 g of ice, 30 mL of acetic acid, and 150 mL of  $\text{CHCl}_3$ . The vigorous stirring was continued for 2 hours. The layers were separated. The chloroform solution was washed with saturated  $\text{NaHCO}_3$  and brine. It was then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield 3.63 g (7.41 mmol) of 122, mp 157-8 °C. NMR ( $\text{CDCl}_3$ ) 0.13 (s, 6H), 0.98 (s, 9H), 1.47 (s, 3H), 1.80-2.46 (envelope, 10H), 3.70 (m, 3H), 3.92 (m, 2H), 4.54 (s, 2H), 4.91 (s, 1H), 7.32 (s, 5H). 90 MHz C-13 NMR ( $\text{CDCl}_3$ ) -3.705, 18.207, 23.144, 25.232, 25.882, 27.313, 29.004, 30.565, 43.504, 54.170, 68.476, 70.557, 73.094, 73.289, 74.264, 83.889, 102.618, 108.861, 127.720, 127.850, 128.370, 145.928. IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ , 3620, 3400, 3010, 2960, 2940, 2860, 1670, 1360, 1250, 1190, 1090, 1045, 920, 870, 830.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-5-oxo-11-oxatricyclo[7.2.1.0]dodecan-2 $\alpha$ , 8 $\beta$ , 12-triol (123)

A 0.10 M THF solution containing 0.27 g (0.55 mmol) of 122 was treated with 0.55 mL of a 1.0 M THF solution of tetra-*n*-butylammonium fluoride. The reaction was stirred at room temperature for 10 hours. It was then poured into 30 mL of ethyl acetate and washed with saturated  $\text{NaHCO}_3$  and brine. The ethyl acetate was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was chromatographed on silica gel (10/1; w/w) using 60/40 ethyl acetate/hexane as the solvent to yield 0.182 g (0.48 mmol) of 123, mp 89-90 °C. NMR ( $\text{CDCl}_3$ ) 1.34 (s, 3H), 1.68-2.46 (envelope, 7H), 3.04 (m, 3H), 3.70 (m, 4H), 4.58 (s, 2H), 4.74 (s, 1H),

7.34 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 22.108, 22.433, 25.621, 28.483, 29.848, 36.156, 39.993, 48.316, 56.445, 68.281, 72.247, 73.158, 73.678, 83.237, 98.065, 127.979, 128.564, 137.018, 213.690. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3400, 3020, 2980, 2880, 1710, 1460, 1240, 1170, 1100, 1050, 910, 850.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2 $\alpha$ , 8 $\beta$ , 12-triacetoxy-5-oxo-11-oxatricyclo[7.2.1.0]dodecane (124)

To a 0.10 M CH<sub>2</sub>Cl<sub>2</sub> solution of 0.26 g (0.69 mmoles) of 123 was added 0.42 g (4.15 mmoles) of triethylamine, 0.352 g (3.45 mmoles) of acetic anhydride, and 0.017 g (0.14 mmoles) of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 10 hours. The excess acetic anhydride was destroyed by adding 0.5 mL of CH<sub>3</sub>OH and allowing the reaction to stir for an additional 10 minutes. The reaction was poured into 25 mL of ether and washed with H<sub>2</sub>O, 1N HCl, saturated NaHCO<sub>3</sub>, and brine. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to yield 0.346 g (0.69 mmoles) of 124. NMR (CDCl<sub>3</sub>) 1.30 (s, 3H), 1.78 (m, 2H), 2.00 (s, 3H), 2.08 (s, 3H), 2.13 (s, 3H), 2.16-2.78 (envelope, 7H), 3.08 (dd, 1H, J = 7 and 12 Hz), 3.50 (m, 2H), 4.52 (s, 2H), 4.86 (d, 1H, J = 5 Hz), 5.20 (m, 1H), 5.74 (s, 1H), 7.32 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 20.807, 22.173, 23.475, 24.711, 26.532, 35.376, 39.928, 46.366, 53.649, 69.451, 70.947, 72.312, 72.703, 83.823, 95.919, 127.394, 128.044, 137.799, 168.948, 169.274, 208.292. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>, 3020, 2960, 2860, 1750-1720, 1710, 1450, 1370, 1220, 1090, 995, 960.

Preparation of (4 $\alpha$ )-10 $\alpha$ -(2-Ethyl Benzyl Ether)-1 $\alpha$ -methyl-2 $\alpha$ ,8 $\beta$ -triacetoxy-5-oxo-11-oxatricyclo[7.2.1.0]dodecane (125)

A 0.05 M CH<sub>2</sub>Cl<sub>2</sub> solution of 0.346 g (0.69 mmol) of 124 was treated with 0.088 g (0.76 mmol) of triethylsilane. To this was added dropwise over a period of 1 minute 0.11 g (0.76 mmol) of boron trifluoride etherate. The reaction was stirred at room temperature for 3 hours. To the reaction was added 5 mL of saturated NaHCO<sub>3</sub> solution. The solution was stirred vigorously for 15 minutes. The reaction was extracted twice with ether. The combined ether extractions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was chromatographed on silica gel (10/1; w/w) using hexane/ethyl acetate as the solvent to yield 0.27 g (0.61 mmol) of 125. NMR (CDCl<sub>3</sub>) 1.24 (s, 3H), 1.34 (m, 2H), 1.86 (m, 2H), 2.02 (s, 3H), 2.14 (s, 3H), 2.18-2.66 (envelope, 5H), 3.02 (dd, 1H,  $J$  = 7 and 12 Hz), 3.50 (m, 4H), 4.52 (s, 2H), 4.84 (d, 1H,  $J$  = 6 Hz), 5.02 (m, 1H), 7.34 (s, 5H). 90 MHz C-13 NMR (CDCl<sub>3</sub>) 21.133, 21.263, 22.108, 24.126, 25.752, 28.418, 35.831, 41.944, 50.723, 51.178, 70.101, 71.987, 73.223, 73.808, 73.938, 82.522, 127.784, 128.434, 138.124, 169.404, 169.794, 209.788. IR (film) cm<sup>-1</sup>, 3040, 2980, 2880, 1735, 1710, 1450, 1370, 1230, 1100, 1040, 1010, 940, 860, 735, 695.

## CONCLUSION

The feasibility of performing an intermolecular  $[4 + 2]$  cycloaddition reaction followed by an intramolecular  $[4 + 2]$  cycloaddition reaction has been demonstrated. The "timed Diels-Alder reaction" is useful for the rapid construction of the fluorenone skeleton and should prove valuable for the preparation of substituted fluorenones for which selective synthetic methods are not presently available. In the attempt to extend the "timed Diels-Alder reaction", an elegant but impractical synthesis of dimethyl phthalate has been discovered.

The Diels-Alder reaction of in situ generated quinones should find general applicability in systems other than the quassinoids. It provides an efficient means for the preparation of large quantities of Diels-Alder adducts which can be converted into useful intermediates for the preparation of the biologically active quassinoids.

Both the "timed Diels-Alder reaction" and the Diels-Alder reaction of in situ generated quinones are significant additions to the ever growing plethora of information concerning the  $[4 + 2]$  cycloaddition reaction. They should also prove to be useful additions to the arsenal of any synthetic chemist engaged in the battle to construct complex organic molecules.

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